201-14391

NCIC HPV
Sent by: Mary-Beth Weaver

04/09/2003 09:34 AM

To: Peter Wendolkowski/DC/USEPA/US@EPA, NCIC HPV@EPA
cc: Mary-Beth Weaver/DC/USEPA/US@EPA, Vanessa Williams/DC/USEPA/US@EPA, Ralph Northrop/DC/USEPA/US@EPA
cc: Mary-Beth Weaver/DC/USEPA/US@EPA, Vanessa Williams/DC/USEPA/US@EPA, Ralph Northrop/DC/USEPA/US@EPA
Subject: HPV SUbmission of Mononitroaniline Category Dossier

"Johannsen, Frederick R" <frjoha@solutia.com> on 11/15/2002 10:43:04 AM

To: Rtk Chem/DC/USEPA/US@EPA
cc: "Downes, James E" <jedown@solutia.com>
Subject: HPV SUbmission of Mononitroaniline Category Dossier

Herewith attached is the submission of our letter, Category Test Plan and Robust Summaries

<<HPVmononitroanilinetrans.doc>> <<HPV MononitroanilinesII.doc>> <<ona.rtf>> <<pna.rtf>>

- HPVmononitroanilinetrans.doc
- HPV MononitroanilinesII.doc
- ona.rtf
- pna.rtf

Solutia Inc.
575 Maryville Centre Drive
St. Louis, MO 63141

P.O. Box 66760
St. Louis, MO 63166-6760

November 15, 2002

Christine Todd Whitman, Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program
In re: HPV Challenge Program
AR-201

Benzeneamine, 2-nitro
CAS Number 88-74-4

Benzeneamine, 4-nitro
CAS Number 100-01-6

Solutia, Inc., Company Registration Number , is pleased to submit the attached Test Plan and Robust Summaries for the Category Mononitroanilines (consisting of Benzeneamine, 2-nitro with CAS No. 88-74-4 and Benzeneamine, 4-nitro, with CAS Number 100-01-6) as a part of our commitment to the EPA High Production Volume Challenge Program (AR-201).

The attached files are:

1. This cover letter in MS Word 2000
2. Category Test Plan in MS Word 2000
3. Robust Summaries (IUCLID format) for both chemicals in this Category in MS Word 2000

The complete matrix of SIDS data elements, including physical/chemical properties and results of biological and toxicology studies, indicate that no additional testing is required.

Please contact me at 314-674-8815 if there are any questions relating to this submission.

Sincerely,

Frederick R. Johannsen

HIGH PRODUCTION VOLUME (HPV)

CHEMICAL CHALLENGE PROGRAM

TEST PLAN

For the

MONONITROANILINE CATEGORY

CAS Number 88-74-4; Benzeneamine, 2-nitro-

CAS Number 100-01-6; Benzeneamine, 4-nitro-

Prepared by:

Solutia Inc. Registration No.

575 Maryville Centre Drive,
St. Louis, Missouri 63141

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EXECUTIVE SUMMARY

Solutia Inc. voluntarily submits the following Category Justification, Screening Information Data (Robust Summaries) and Test Plan for review under the Environmental Protection Agency's High Production Volume (HPV) Chemicals Challenge Program. The category, entitled "Mononitroanilines" consists of two members, Benzeneamine, 2-nitro, also known as 2-Nitroaniline (CAS No. 88-74-4) and Benzeneamine, 4-nitro, also known as 4-Nitroaniline (CAS No. 100-01-6). This category is justified on the basis of chemical structure similarity, as well as similarity of basic screening data, as provided in an initial assessment of physico-chemical properties, environmental fate and human and environmental effects.

A substantial amount of data exists to evaluate the potential hazards associated with this Category of chemicals. Use of key studies available from data already developed or derived from recommended estimation models provide adequate support to characterize each Endpoint in the HPV Chemicals Challenge Program without the need for additional testing.

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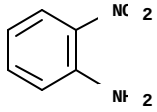
TEST PLAN FOR MONONITROANILINES

I. INTRODUCTION AND IDENTIFICATION OF CATEGORY MEMBERS

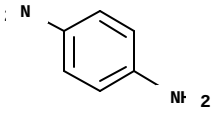
Under EPA's High Production Volume (HPV) Chemicals Challenge Program, Solutia Inc. has committed to voluntarily compile basic screening data on two chemicals of similar structure, namely Benzeneamine, 2-nitro (known as 2-nitroaniline or ONA) and Benzeneamine, 4-nitro (known as 4-nitroaniline or PNA). Solutia Inc. believes that a category of Mononitroanilines is scientifically justifiable. The data included in this category involve physicochemical properties, environmental fate, and human and environmental effects of the chemicals in this Category, as defined by the Organization for Economic Cooperation and Development (OECD). Most of the information provided comes from existing data developed on behalf of Solutia Inc., much of which has already been submitted to the US EPA under auspices of sections of the Toxic Substances Control Act and is available through TSCATS; additional information can be found in the published scientific literature or from recommended estimation models. This submission fulfills Solutia's obligation to the HPV Challenge Program for these two chemicals.

A. Structure and Nomenclature

The members of this family of Mononitroanilines, include the following chemicals:



a. Benzeneamine, 2-nitro-
CAS No. 88174-4
Synonyms: 2-Nitroaniline; 1-Amino-2-nitrobenzene; ortho-nitroaniline; o-nitroaniline; ONA;



b. Benzeneamine, 4-nitro-
CAS No. 100-01-6
Synonyms: 4-nitroaniline; 1-Amino-4-nitrobenzene;
para-nitroaniline; p-nitroaniline; PNA;

B. Manufacturing & Use

Both p-Nitroaniline (PNA) and o-Nitroaniline (ONA) are manufactured by a single US producer, Solutia Inc., at a single manufacturing site in an essentially closed, continuous process. Only a few employees are involved in the manufacturing operations and have minimal potential for skin or airborne exposure, which occur chiefly during material transfer operations.

Both PNA and ONA produce methemoglobinemia in human and animals (Linch, 1974; Watanabe et al, 1976) and are known to be hazardous after dermal contact. Addition of the nitro group in the *para* position to the aniline molecule results in the formation of the more toxic compound. To minimize the potential for adverse health effects due to methemoglobinemia resulting from occupational exposure via inhalation or skin absorption, a TLV ® of 3 mg/m^3 has been established for PNA (ACGIH, 2001). While comparative toxicity and occupational experience indicate that ONA produces less toxicity and a lower risk of methemoglobinemia, an internal Solutia Inc. occupational standard of 3 mg/m^3 has also been set for this chemical. In both cases, specific manufacturing procedures and practices have been established to minimize occupational exposure potential.

Both Mononitroanilines, para-Nitroaniline (PNA) and ortho-Nitroaniline (ONA), are important chemical intermediates which serve as basic building blocks for the ultimate manufacture of numerous industrial chemicals. For example, PNA is utilized in preparation of antioxidants, antiozonants, and dyes and pigments while ONA is converted to polymer additives, veterinary pharmaceuticals and water-treatment chemicals.

PNA and ONA are sold to a limited number of customers at a few US processing sites for the express purpose of full chemical conversion into other industrial chemicals. There are no known or suspected consumer exposures to either PNA or ONA resulting from TSCA-related activities, as they are fully consumed as chemical intermediates. Loss to the atmosphere or from non-POTW aqueous streams during manufacturing or processing is minimal. Hence, very limited occupational or environmental exposure is expected to occur.

II. CATEGORY JUSTIFICATION

For purposes of the HPV Challenge Program, EPA has provided guidance as to the definition and justifications to be used in selection of a chemical Category (US EPA, 1999c). The definition states that a chemical category should be "a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity". Solutia Inc. has opted to form the Mononitroaniline Category with this guidance in mind.

Common Structure

The two chemicals selected for inclusion in this category are isomeric forms of the same base chemical, nitroaniline. Hence, they are of common structure.

Common Functional Groups

Each of these amino compounds are aromatic hydrocarbons for which one benzene ring hydrogen has been replaced by a nitro (NO2) radical and one benzene ring hydrogen further replaced with an amino (NH2) group; the position (either *ortho* to or *para* to the nitro grouping) of the ring placement of the amino grouping is the only structural difference between these two chemicals. For the most part, these compounds are similar in chemical properties, as well as in their pharmacological or toxicological effects. As such these effects are modified to a greater or lesser degree by the location of the substituent radical (Beard and Noe, 1982).

Similar or even Identical Properties or Hazards

Physicochemical properties of these two isomeric forms of the same chemical are quite similar. The physical form of both is crystalline and their molecular weights and specific gravity are identical. Other parameters are similar, but not identical.
A summary of available physicochemical data can be found in Table 3.

Environmental Fate data are summarized in Table 4. As shown, a large body of published information exists in this data category. Whether measured or estimated, there appears close agreement in each of the HPV Endpoints recorded for both chemicals in this category.

Comparative aquatic toxicity of both members of this Category can be found in Table 5. As shown, a similar degree of toxicity has been observed across the multiple test species included in this dataset.

Tables 6 - 9 summarize the comparative mammalian toxicity of both of these chemicals. It is well recognized that both chemicals possess a similar mode of action. Their toxicity is characterized by a common and outstanding property, i.e., the ability to form methemoglobin (Beard and Noe, 1982) in both humans and animals. However, there are marked species differences in susceptibility to methemoglobinemia with humans being decidedly more affected than rodent species. Thus, results of acute toxicity studies in rodents are not considered fully representative of the high acute toxicity to humans which can be elicited by these chemicals. On the basis of past human experience, where dermal contact or inhalation exposures resulted in incidences of methemoglobinemia, unusually diligent care has been taken to insure proper handling of both chemicals (each treated equally) during manufacture, shipment, disposal and use.

Thus, similarities in the biological mode of action and the extensive comparative data sets presented support use of a Category approach for these chemicals.

III. TEST PLAN RATIONALE

The information obtained and included to support this Test Plan have come from either 1) internal studies conducted by/or for Solutia Inc. (or its predecessor Monsanto Co.), 2) have been extracted from the scientific literature either as primary references or as found in well-accepted, peer-reviewed reference books, or 3) were estimated using environmental models accepted by the US EPA (1999b) for such purposes. This initial assessment includes information on physicochemical properties, environmental fate, and human and environmental effects associated with both members of this Category. The data used to support this program include those endpoints identified by the US EPA (1998); key studies have been identified for each data Endpoint and summarized in Robust Summary form and included in Section VII of this dossier.

All studies were reviewed and assessed for reliability according to standards specified by Klimisch *et al* (1997), as recommended by the US EPA (1999a). The following criteria were used for codification:

1. Reliable without Restriction - Includes studies which comply with US EPA and/or OECD-accepted testing guidelines, which were conducted using Good Laboratory Practices (GLPs) and for which test parameters are complete and well documented,

2. Reliable with Restriction – Includes studies which were conducted according to national/international testing guidance and are well documented. May include studies conducted prior to establishment of testing standards or GLPs but meet the test parameters and data documentation of subsequent guidance; also includes studies with test parameters which are well documented and scientifically valid but vary slightly from current testing guidance. Also included were physical-chemical property data obtained from reference handbooks as well as environmental endpoint values obtained from an accepted method of estimation (i.e. EPIWIN).

3. Not Reliable – Includes studies in which there are interferences in either the study design or results that provide scientific uncertainty or where documentation is insufficient.

4. Not Assignable – This designation not used in this dossier.

Those studies receiving a Klimisch rating of 1 or 2 are considered adequate to support data assessment needs in this Dossier. Those key studies selected for inclusion are considered typical of the Endpoint responses observed in other studies of a similar nature and design, which were identified during our search of the literature; additional references can been found in the current ECB IUCLID dossiers for p-Nitroaniline (2000) and o-Nitroaniline (2000), as referenced below.

IV. TEST PLAN SUMMARIES AND CONCLUSIONS

The referenced available data for each Category member has been placed in an Endpoint-specific matrix and summarized individually in Table 1 (PNA) and Table 2 (ONA). Substantial data exists for each chemical to evaluate its potential hazards in this screening level assessment. Where an HPV Endpoint has been untested, the need for testing has been assessed (1) with the understanding that these chemicals behave in a similar and/or predictable manner, and (2) by interpolation (i.e. Read-Across technique) between data from other key studies already available. Thus, we have used preexisting data, where possible, to support our assessment of potential hazards of the chemicals in this category and avoid the unnecessary testing of additional laboratory animals.

Conclusion: All HPV Endpoints have been satisfied for both PNA and ONA with data from studies that were either well documented, used OECD guideline methods and conducted in accord with GLPs, or were estimated from acceptable estimation modeling programs. Known properties or use of Read Across" were

used sparingly to support a limited number of endpoints. Hence, no further testing for any of the HPV endpoints is deemed necessary (Tables 1 and 2).

Physical-chemical property values (Melting Point, Boiling Point, Vapor Pressure, Partition Coefficient and Water Solubility) for both PNA and ONA were obtained from reputable references and cited as an Accepted or Peer Reviewed value in the Hazardous Substances Data Bank – p-Nitroaniline (2002) or the Hazardous Substances Data Bank – o-Nitroaniline (2002). They were given a classification of "2-Reliable with restrictions".

Environmental Fate values describing Photodegradation (PNA only) and Transport (Fugacity) for both PNA and ONA were obtained using a computer estimation – modeling program (EPIWIN, 2002) recommended by EPA and classified as "2-Reliable with restrictions"; Photodegradation study data was used for ONA and Biodegradation data for PNA and ONA were characterized in a well documented study conducted according to ASTM/EPA guidelines, which since have been codified and are similar to OECD test #301 guidance and thus also classified as "2-Reliable with restrictions". No Stability in Water (hydrolysis) data was found for either ONA or PNA, nor could values be calculated using EPIWIN, as these chemicals are know to be resistant to hydrolysis.

Ecotoxicity Endpoints for PNA and ONA have been fulfilled with studies that were conducted either according to OECD test guidelines or followed US EPA test guidance consistent with OECD test guidelines. All studies were well documented and were designated "1-Reliable without restriction".

Mammalian Toxicity Endpoints, including Acute Toxicity, Repeated Dose Toxicity, Ames Mutagenicity and Chromosomal Aberration Testing, for both PNA and ONA have been fulfilled by way of tests that either conformed directly to OECD test guidance or followed test designs similar to OECD guidance.

The Acute Toxicity Endpoint for ONA is supported by an acute inhalation study that followed OECD guideline 403 and was considered "1-Reliable without restriction". PNA is supported by an acute oral toxicity study of sound scientific merit and designated "2-Reliable with restrictions", as small differences existed in methodology vs. OECD # 401.

A 90-Day oral rat toxicity study meeting OECD test guideline # 408, and deemed "1-Reliable without restriction" supports the Repeated Dose Endpoint for PNA. Tandem (initial and subsequent follow-on study) 4-week inhalation studies conducted with ONA jointly meet OECD test guideline 412 and thus fulfill this data Endpoint;

Ames mutagenicity tests with PNA and ONA followed study designs equivalent to OECD guideline # 471 and have been designated "1-Reliable without restriction" and "2-Reliable with restrictions", respectively. Mouse Micronucleus Assays, conducted with PNA and ONA, respectively, followed OECD test guideline # 474 and were each designated "1-Reliable without restriction".

A 2-Generation Reproduction Study fulfills the HPV requirements for the last mammalian toxicity Endpoint for PNA. This study meets OECD test guideline # 416 and has been classified as "1-Reliable without restriction". No similar Reproductive toxicity testing has been identified with ONA, although a fully acceptable ("1-Reliable without restriction") rat developmental toxicity study with ONA has been conducted. Use of the "Read-across" concept (i.e. determination of the need to fulfill this data requirement based on substitutive use of available data from a similar, closely related chemical…in this case PNA) obviates the need for additional testing for ONA. While Repeated Dose Toxicity testing with ONA appears insufficient in duration (only 4 weeks rather than 13 weeks) to meet EPA/OECD guidance for completion of the Reproductive Toxicity Endpoint (US EPA, 1998), it is noteworthy that there is an absence of testicular effects seen (1) with ONA in multiple studies of less than 90 days duration (by two exposure routes) and (2) in numerous studies of greater than 90 days duration (including chronic testing) with PNA.

Based on the conclusions as outlined above on HPV Endpoint assessment, following is a tabular depiction of data availability and testing recommendations for p-Nitroaniline (PNA) (Table 1) and o-Nitroaniline (ONA) (Table 2).

Table 1. Test Plan Matrix for para-Nitroaniline (PNA)

	Info. Avail.	OECD	GLP	Other Study	Estimat. Method	Accept-Able ?	Testing Recomm.
PHYSICAL CHEMICAL							
Melting Point	Y	N	N	R	-	Y	N
Boiling Point	Y	N	N	R	-	Y	N
Vapor Pressure	Y	N	N	R	-	Y	N
Partition Coefficient	Y	N	N	R	-	Y	N
Water Solubility	Y	N	N	R	-	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	N	N	-	Y	Y	N
Stability in Water	N	N	N	-	N	-	N
Biodegradation	Y	N	N	Y	-	Y	N
Transport between Environmental Compartments (Fugacity)	Y	N	N	-	Y	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	Y	Y	-	-	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	Y	Y	-	-	Y	N
Acute Toxicity to Aquatic Plants	Y	Y	L	-	-	Y	N
MAMMALIAN TOXICITY							
Acute Toxicity	Y	N	N	Y	-	Y	N
Repeated Dose Toxicity	Y	Y	Y	-	-	Y	N
Genetic Toxicity – Mutation (Ames)	Y	Y	Y	-	-	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	Y	Y	-	-	Y	N
Reproductive Toxicity	Y	Y	Y	-	-	Y	N
Developmental Toxicity	Y	Y	Y	-	-	Y	N

Y = Yes; N = No; L = Likely, but not specified; R = Reputable Reference;
ND = No information available; - = Not applicable

Table 2. Test Plan Matrix for ortho-Nitroaniline (ONA)

	Info. Avail.	OECD	GLP	Other Study	Estimat. Method	Accept-Able ?	Testing Recomm.
PHYSICAL CHEMICAL							
Melting Point	Y	N	N	R	-	Y	N
Boiling Point	Y	N	N	R	-	Y	N
Vapor Pressure	Y	N	N	R	-	Y	N
Partition Coefficient	Y	N	N	R	-	Y	N
Water Solubility	Y	N	N	R	-	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	N	N	Y	-	Y	N
Stability in Water	N	N	N	-	N	-	N
Biodegradation	Y	N	N	Y	-	Y	N
Transport between Environmental Compartments (Fugacity)	Y	N	N	-	Y	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	Y	L	-	-	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	Y	Y	-	-	Y	N
Acute Toxicity to Aquatic Plants	Y	Y	L	-	-	Y	N
MAMMALIAN TOXICITY							
Acute Toxicity	Y	Y	Y	-	-	Y	N
Repeated Dose Toxicity	Y	Y	Y	-	-	Y	N
Genetic Toxicity – Mutation (Ames)	Y	N	N	Y	-	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	Y	Y	-	-	Y	N
Reproductive Toxicity	N	-	-	-	-	C	N
Developmental Toxicity	Y	Y	Y	-	-	Y	N

Y = Yes; N = No; L = Likely, but not specified; R = Reputable Reference;
C = Read-across from available data on PNA; - = Not applicable

V. Data Set Summaries and Evaluations

The key studies used in this assessment to fulfill the HPV requirements for both PNA and ONA have been placed in an Endpoint-specific matrix, and further discussed below. As a number of studies supporting many of these Endpoints exist for each Mononitroaniline, key studies were selected based on their representative presentation of data characterization as well as their reliability. Robust Summaries for each study referenced can be found in Section VII of this dossier.

A. Chemical/Physical Properties

A large number of studies are available summarizing the **Physical-Chemical** properties associated with both of these Mononitroanilines. They can be found in ECB IUCLID Dossiers for p-Nitroaniline (2000) and o-Nitroaniline (2000). Table 3 contains those values that are considered to best depict the consensus of results found in most key sources used to define the characteristics of each of these Mononitroanilines. They have been obtained from reputable reference books and cited in peer-reviewed data sources; thus, they are considered "2-Reliable with restrictions". A Robust Summary has been prepared for each of the references included in Table 3.

In summary, PNA and ONA are solid entities at room temperature and possess low vapor pressures. They have a moderate partition coefficient and are moderately soluble in water.

Conclusion: Sufficient data exists to fully characterize the Physical-Chemical properties of each of these Mononitroanilines. All HPV data requirements for this Endpoint have been met and no further data collection is planned.

Table 3. Selected Physical Properties of Mononitroanilines

Chemical	Boiling Pt. (^{o}C.)	Melting Pt. (^{o} C.)	Vapor Pressure (hPa @ 25 ^{o}C)	Water Solubility (mg/L)	Partition Coeffient (Log Kow)
o-Nitroaniline CAS No. 88-74-4	284	71.5	0.0368	1470 @ 25 ^{o} C.	1.85
p-Nitroaniline CAS No. 100-01-6	332	146	0.0053	724 @ 25 ^{o} C.	1.39

B. Environmental Fate and Biodegradation

A well-conducted Semi-Continuous Activated Sludge (SCAS) Biodegradability study has been conducted to compare the biodegradation potential of PNA and ONA; it has been summarized in the Robust Summary section of this Dossier and cited in Table 4 below.

While conducted prior to inception of standardized international guidelines for **Biodegradability** testing and GLPs, this study followed similar standards for conduct subsequently codified into OECD guideline 301 and GLP documentation. Thus, this study is considered to be "2-Reliable with restrictions". We have incorporated the use of estimation models found in EPIWIN (2002) for determination of **Photodegradation** for PNA and Transport Between Environmental Compartments (**Fugacity),** using model Level III, and employing measured values, where possible, as recommended by the US EPA. Thus, they have been classified as "2-Reliable with restrictions". The Photodegradation study with ONA was classified as "2-Reliable with restriction". These estimates have also been included in Table 4 and are cited in the Robust Summary section of this Dossier; data entries into the Level III fugacity model have been included in the Robust Summaries for validation of output. No values have been identified for either ONA or PNA to define their **Stability in Water** (hydrolysis). Further no such values could be calculated using EPIWIN (2002) as both ONA and PNA have only aromatic nitro and aromatic amine functional groups, both of which are listed in Lyman et al. (1990) as Generally Resistant to Hydrolysis. Thus, "[t]esting for Stability in Water is not needed for substances generally recognized to have molecular structures or possess only functional groups that are generally known to be resistant to hydrolysis" (OECD, 2002).

Conclusion: Sufficient information exists to characterize the Environmental Fate and Biodegradation of each of these Mononitroanilines. Where experimental data do not exist, use of an estimation model (EPIWIN) recommended by EPA provided necessary information or the rationale lack of need for testing has already been recognized. Thus, all HPV data requirements for this Endpoint are met and no further data collection is planned.

Table 4. Comparison of Biodegradation Endpoints for Category Members

Chemical	Biodegradation Rate	Stability in Water	Photodegradation	Fugacity (%)
o-Nitroaniline CAS No. 88-74-4	7% Primary Degrad. (SCAS)	n.d.	T1/2 = 9.5 hr	Air- 0.5 Water- 36.1 Soil- 63.3 Sediment-0.1
p-Nitroaniline CAS No. 100-01-6	82% Primary Degrad. (SCAS)	n.d.	T1/2 = 9.5 hr	Air- 0.6 Water- 36.8 Soil- 62.6 Sediment-0.01

n.d. = no data available

To summarize the Environmental fate of these Mononitroanilines, PNA and ONA should readily degrade in the vapor phase in the ambient atmosphere via reaction with photochemically producted OH- radicals and thus exhibit a short half-life (Meylan and Howard, 1993)(Table 4). Aromatic amines and nitroaromatics are generally resistant to aqueous environmental hydrolysis (Lyman et al, 1982); therefore, estimations to determine hydrolysis in water could not be determined from use of an EPIWIN program

as no hydrolysable groups were found on the molecule (Table 4). Even in activated sludge testing, ONA is considered resistant to biodegradation, while PNA is considered "readily biodegradable" (Table 4). Similar studies cited in the IUCLID dossiers (ECB IUCLID on ONA, 2000, and PNA, 2000), also indicate a similar pattern of biodegradation capacity. Regression-derived estimates and experimentally-derived values of studies summarized in their respective IUCLID dossiers (2000) indicate that the bioconcentration potential of both ONA and PNA are low. Therefore, aquatic hydrolysis, volatilization from the aqueous environment and bioconcentration are of little importance (Lyman et al, 1982).

C. Aquatic Toxicity

Several references to acute fish, invertebrate and algal toxicity can be found in the ECB IUCLID documents for PNA (2000) and ONA (2000). Data presented in Table 5, and summarized in the Robust Summary section VII, depict the level of toxicity generally observed for these Endpoints within the overall dataset. Each of the studies selected was conducted according to OECD test guidelines (# 201, 202, or 203) or according to US EPA test guidance (ASTM/EPA) consistent with international guidance. Thus, they are considered "1-Reliable without restriction" even though no specific mention was made of their conduct employing GLPs. As these studies were published in peer-reviewed journals and were specifically identified as having been conducted in accord with OECD test methods, it is reasonable to assume that GLP guidance was also followed.

Conclusion: Sufficient data exists to fully characterize the Acute Aquatic Toxicity properties of each of these Mononitroanilines. All HPV data requirements for this Endpoint have been met and no further data collection is planned for either material.

Based on the values presented in Table 5, both PNA and ONA have a similar degree of acute toxicity to all three aquatic species; studies with *D. magna* proved to produce the lowest levels of toxicity, comparatively. Overall, PNA and ONA are considered to possess a low order of ecotoxicity.

Table 5. Comparison of Aquatic toxicity parameters for category members

Chemical	Fish LC 50 (mg/L)	Invertebrate LC50 (mg/L)	Algae EC50 (mg/L)
o-Nitroaniline CAS No. 88-74-4	19.5 (96-hr) (Zebrafish)	14.5 (48-hr) (Daphnia magna)	64.5 (48- hr)
p-Nitroaniline CAS No, 100-01-6	45 (96-hr) (R. trout)	20.0 (48-hr) (Daphnia magna)	54.9 (48-hr)

D. Mammalian Toxicity

1.0 Acute Toxicity

Key acute toxicity studies by multiple exposure routes were chosen from a number of other acute reports to represent the highest (most toxic) acute toxicity values identified from reliable sources. This was done specifically since acute toxicity studies with some laboratory animals are not considered sufficiently predictive of the acute hazards of these nitroanilines to humans, due to the resistance observed in lab animals to development of methemoglobinemia. All studies included in Table 6 were conducted specifically or in general agreement with OECD acute toxicity testing guidance and are considered either "1-Reliable without restriction" or "2-Reliable with restrictions". While individual studies were identified as key studies (inhalation study for ONA and oral study for PNA) to fulfill this HPV Endpoint for each of the Category members, reliable studies involving other exposure routes are included as Supplemental information to provide as complete a summary as possible for this assessment. Other acute toxicity reports are also cited in the ECB IUCLID dossiers for both PNA (2000) and ONA (2000).

Table 6. Acute Mammalian Toxicity for Category members

Chemical	Oral LD50 (mg/kg)	Dermal LD50 (mg/kg)	Inhalation LC50 (mg/L)
o-Nitroaniline CAS NO. 88-74-4	2,050 (rat)	> 7,940 (rabbit)	> 2529 mg/m3 (rat) - 4-hr. expos.
p-Nitroaniline CAS No. 100-01-6	1,400 (rat)	> 7,940 (rabbit)	-

Conclusion: Sufficient data from well-documented studies exist to meet the Acute Toxicity data set requirements for both members of this Category. Hence, no further acute toxicity testing is planned.

2.0 Repeated Dose Toxicity

PNA, the sentinel chemical in this Category, has been extensively evaluated in Repeated Dosing studies of various durations and by different exposure routes. Studies which fulfill the requirements for this HPV Endpoint are summarized in Table 7. Additional repeated dose studies, including a chronic oral rat study, a 13-week oral toxicity study in mice and a chronic toxicity/carcinogenicity study in mice are included in the ECB IUCLID – PNA (2000) dossier. The key study selected to fulfill this HPV Endpoint was the 90-day oral study in rats, which followed OECD Test Guideline 408 and is considered "1-Reliable without restriction".

A consistent pattern of repeated dose PNA toxicity is apparent. Clinical observations, serum chemistry changes, organ weight differences and histopathological findings were all related to methemoglobin formation and compensatory processes that occurred as a

result. Further, these same toxicological effects were seen consistently (and to the exclusion of other effects) after 14 days on test, after 13 weeks of testing, or at interim or final sacrifice after lifetime exposure. Specifically, no treatment-related effects on male or female gonads (reproductive organs) were seen in any of the above studies; thus, these tissues are not considered as target organs for PNA.

Conclusion: The Repeated Dose HPV Endpoint for PNA is complete with conduct of a 13-week oral study in rats and no further testing is needed.

Table 7. Repeated Dose Toxicity Studies with Category Members

Chemical	Study Type	Dosages	Histopathology	Hematology/ Clinical Findings
o-Nitroaniline (ONA) CAS NO. 88-74-4	4-Week Rat inhal. 6 hr/d; 5d/wk 10/sex/group	93 mg/m3 (males only) 73 mg/m3 28 mg/m3 10 mg/m3	No treatment-Related findings	Serum methemoglobin Hematocrit Leukocytes Hemoglobin Erythrocytes Leukocytes Serum calcium Serum calcium NOEL
p-Nitroaniline (PNA) CAS No. 100-01-6	4-Week Rat inhal. 6 hr/d; 5d/wk 10/sex/group	90 mg/m3 30 mg/m3 10 mg/m3	spleen wt. hemosiderosis & hematopoiesis in spleen & liver spleen wt. hemosiderosis & hematopoiesis in spleen spleen wt. hemosiderosis & hematopoiesis in spleen	methemoglobin anemia leukocytes methemoglobin anemia
p-Nitroaniline (PNA) CAS No. 100-01-6	90-Day Oral (gavage) 20/sex/group	30 mg/kg 10 mg/kg 3 mg/kg	hemosiderosis & hematopoiesis in spleen hemosiderosis & hematopoiesis in spleen hemosiderosis & hematopoiesis in spleen	methemoglobin anemia methemoglobin anemia methemoglobin anemia

ONA has been evaluated in a series of two 4-week repeated dose inhalation rat studies designed to provide comparative toxicological evaluation with a 4-week inhalation PNA study conducted concurrently and cited above (Table 7). Due to confounding use of a solvent in the first ONA study, i.e., ethylene glycol monoethyl ether (EGME, i.e. CELLOSOLVE), which was subsequently determined to produce effects on the testes, a follow-up study using a targeted design to assess this endpoint was performed with ONA (without EGME). The initial 4-week study was conducted according to GLPs and met OECD Test Guideline 412 study parameters. Due to the confounding use of EGME, this study is judged as "2-Reliable with restrictions". Specifically, all study parameters measured (clinical signs, body weight, ophthalmology, blood chemistry, hematology, organ weights, microscopic pathology), EXCEPT for effects regarding the testes and the hematology findings are considered reliable. The rationale for this conclusion rests on the fact that all other study endpoints assessed were without effect even up to the highest level tested and hence, no effect of treatment was noted. The hematological effects noted at the high test level were consistent with a methemoglobin-forming chemical and thus were reevaluated (and confirmed as treatment-related) in the follow up study.

In order to assess the hematology and testicular findings seen in the first ONA inhalation study, a follow up study was conducted at two ONA doses, one was the low dose originally used and the other was a dose level in excess of that originally used. The follow-up study used only male rats and measured only hematological effects (noted in the earlier study) and testicular effects (weights and histopathology). This time the ONA atmosphere was generated without use of EGME. Results of this study affirmed the effects of ONA on hematology parameters seen in the original study at the high dose level, but also established that no effects on the testes occurred, either macroscopically or microscopically, when ONA alone was used. On this basis, the findings in this second study are considered "1-Reliable without restriction". Thus, the gonadal effects seen in the original study were not reproduced when ONA was retested without use of EGME, even at a higher dose level than used in the first study, and confirmed that the original results were unrelated to ONA treatment. Subsequent to conduct of these studies the effects of EGME on the reproductive system appeared in the scientific literature (Barbee et al., 1984) providing further confirmation of this conclusion. A summary of the two, combined 4-week inhalation studies described above are included in Table 7, and summarized separately in the Robust Summary section of this Dossier.

To summarize, subchronic toxic effects with ONA were equivalent to those seen with PNA albeit to a lesser degree and were consistent with ONA's diminished capacity to produce methemoglobinemia relative to PNA. There were no effects on male or female gonads seen with either Mononitroaniline. Komsta et al (1989) also reported no treatment-related effects associated with any of a comprehensive evaluation of biochemical, hematological and histopathological indices (including a lack of effect on gonads of either sex) following 14-day oral dosing of ONA to rats (ECB IUCLID – ONA, 2000).

Conclusion: Consideration of the two 4-Week inhalation studies in combination, the requirements for the Repeated Dose HPV Endpoint for ONA are complete and no further testing is needed.

3.0 Mutagenicity and Chromosomal Aberrations

Ames Test – p-Nitroaniline

PNA has been examined extensively in the Ames test. While a number of literature citations report the lack of mutagenic activity with PNA, the preponderance of evidence indicates that PNA expresses a weak mutagenic response in tester strain TA98 and the nitroreductase modified TA98NR, with and without metabolic activation (ECB IUCLID-PNA, 2000). A key study selected to fulfill this HPV Endpoint was conducted according to GLPs and conformed to OECD Test Guideline 471. It is considered "1-Reliable without restriction" and has been cited in Table 8 as well as extensively summarized in the Robust Study section of this Dossier.

Other *in vitro* mutagenicity assays conducted with PNA have provided mixed results. PNA was considered positive in the Japanese Rec assay and in a Mouse Lymphoma assay but negative in a CHO cell HGPRT forward gene mutation assay (ECB IUCLID – PNA, 2000); further, no genotoxic activity was reported when PNA was tested in an *in vitro* Unscheduled DNA Synthesis (UDS) assay or in an *in vivo/in vitro* DNA Synthesis test (ECB IUCLID – PNA, 2000). The absence of mutagenic activity was noted when PNA was tested in a secondary tier point mutation assay, the *Drosophila* germ cell test for sex-linked recessive lethal (SLRL) mutations (ECB IUCLID – PNA, 2000).

Conclusion: The Ames test HPV endpoint for PNA was has been fulfilled. Further, the preponderance of the mutation data with mammalian cells and secondary tier assays indicate that PNA does not pose a mutagenic risk and no further testing is warranted.

Ames Test - o-Nitroaniline

A considerable number of Ames test assays have been conducted with ONA, several which fully meet international test method guidance (ECB IUCLID – ONA, 2000). Results have been negative (i.e. no mutagenic activity) in every *Salmonella* tester strain used, with and without metabolic activation. An Ames test conducted according to guideline OECD # 471 was selected to support this HPV Endpoint. It has been given a rating of "2-Reliable with restrictions" in that, while well documented, no information as to its compliance with GLPs was included in the literature citation from which it was taken.

Conclusion: The Ames Test Category Endpoint for ONA has been met and no further testing should be considered for the gene point mutation endpoint for this chemical.

Table 8. Genetic Toxicity of Category Members

Chemical	Ames Test- TA98, 100, 1535, 1537 +/- activation	Cytogenetics In Vitro	Cytogenetics In Vivo
o-Nitroaniline CAS NO. 88-74-4	Neg. w & w/o S-9.; all strains	Ambiguous- CHO Cells	Negative – mouse micronucleus assay (IP)
p-Nitroaniline CAS No. 100-01-6	Pos. TA98, w/o S-9. (boarder-line w S9)	Ambiguous - CHO Cells	Negative – mouse micronucleus assay (IP)

Chromosomal Aberrations - p-Nitroaniline

Several *in vivo* and *in vitro* studies have been conducted to assess the potential clastogenicity of PNA (ECB IUCLID – PNA, 2000). A Mouse Micronucleus test, fully complying with OECD Test Guideline 474 and considered "1-Reliable without restriction", is presented in Table 8 as the key study to fulfill this HPV Endpoint requirement. A Robust Summary of this study can be found in section VII of this Dossier. No mutagenic response was seen in this secondary tier *in vivo* study.

Two *in vitro* CHO cell chromosomal aberration studies, including one which also evaluated Sister Chromatid Exchange potential of PNA, are also reported in the ECB IUCLID – PNA (2000). Weak, sometimes nonreproducable positive responses were observed at cytotoxic dosages while the potential influence of pH and ionic strength were not considered. Hence, these studies are considered to provide ambiguous results and of insufficient reliability for use in this assessment.

Conclusion: On the basis of a highly reliable Micronucleus study available with PNA, no additional testing is needed to fulfill this HPV Endpoint.

Chromosomal Aberrations - o-Nitroaniline

Two independently conducted Mouse Micronucleus tests, each administering ONA by the IP injection route, substantiated the absence of increased micronuclei formation at any test level (ECB IUCLID-ONA, 2000). While both of these studies meet study conduct and reporting sufficient to be considered fully reliable, we have cited (Table 8) and summarized (Robust Summary) one study as representative and thus the key study to fulfill this HPV Endpoint. This study fully complies with OECD Test Guideline 474, was conducted according to GLPs, and thus is considered "1-Reliable without

restriction". The ECB IUCLID for ONA also cited an article reporting results of an *in vitro* chromosomal aberration study, as well as a mouse micronucleus assay using oral dosing. This report is considered unreliable as the paper itself questioned the legitimacy of the results. Thus, we have not included that report in this Dossier.

Conclusion: Based on availability of a fully reliable Mouse Micronucleus test, this HPV Endpoint for ONA has been fulfilled. No additional testing is warranted.

4.0 Reproductive and Developmental Toxicity

The Reproductive and developmental toxicity associated with the chemicals in this Category have been well studied. The sentinel chemical in this group, PNA, has undergone extensive testing for developmental toxicity in two species (rat and rabbit) and has been evaluated in a two-generation rat reproduction study (Nair et al, 1985, 1990). It has also been included in a preliminary developmental toxicity screen in mice (Hardin et al., 1987). Each of the PNA studies reported in Nair et al (1985) have been assess as "1-Valid without restriction" as they fully met OECD testing and GLP guidance. The Two Generation rat Reproduction study is considered the key study to fulfill this HPV Endpoint for PNA, while the developmental toxicity studies are included as Supplemental information. Each of the adequately conducted studies has been summarized in Table 7.

Conclusion: Based on completion of the Two-Generation Rat Reproduction Study with PNA, no further testing is needed to meet this HPV Endpoint for this chemical and none is planned.

ONA has been evaluated in a comparative (to PNA) rat teratology study. This study has also been evaluated as being "1-Valid without restriction" and has been summarized in Table 7.

We believe sufficient data exist in this Category to provide an adequate evaluation for ONA based on similarity of mammalian toxicity between ONA and PNA and through use of corresponding reproductive toxicity data available on PNA. While no reproductive toxicity study has been conducted on ONA, a fully acceptable developmental toxicity study is available. Results of 4-week repeated dose studies by 2 exposure routes with ONA and PNA confirmed that the male and female reproductive organs are not target organs for either chemical. It is recognized that none of the ONA repeated dose studies meet the OECD acceptance criterion of 90 days test duration agreed upon to accommodate this endpoint. However, the following toxicological considerations justify the use of a "Read across" approach, using the PNA reproductive study in rats to substitute for similar unnecessary testing with ONA: (1) the comparative toxicity between ONA and PNA in similarly conducted acute and repeated dose mammalian toxicity studies (noting that ONA was always less toxic than PNA), (2) the lack of significant adverse findings in the ONA

developmental toxicity study, (3) the absence of reproductive effects associated with PNA exposure up to levels inducing other signs of toxicity, (4) extensive subchronic and chronic testing of PNA in multiple species, all of which failed to identify male or female gonads as a target tissue and (5) the highly controlled, closed system manufacturing and use environment associated with ONA already in place to minimize exposure potential and prevent methemoglobinemia.

Thus, we conclude that use of all available data in the Category approach, along with key studies with ONA itself, allows this HPV Endpoint to be completed without further unnecessary testing of ONA.

Table 9. Summary of Developmental Toxicity and Reproduction Studies with Category Members

Chemical	Study Type/Species	Dosage	Observations	Conclusion
o-Nitroaniline (ONA) CAS NO. 88-74-4	Rat Teratology – Gavage 25 /group	600 mg/kg	Maternal Toxicity: Body wt gain Food consump. Physical signs Terata-equivocal	NOEL for Embryotoxicity, Fetotoxicity, Terata (equivocal)
		300 mg/kg	Physical signs only	Absolute NOEL For Terata, embryotoxicity and fetotoxicity and NOAEL for Maternal toxicity
		100 mg/kg	No findings	
p-Nitroaniline (PNA) CAS No. 100-01-6	Rat Teratology – Gavage 25/group	250 mg/kg	Maternal toxicity: Body wt. Gain Physical changes Spleen wt. Embryotoxicity: Resorptions Fetotoxicity: Fetal wts. Terata: External, soft tissue and skeletal	
		85 mg/kg	Maternal toxicity: Physical changes Spleen wt. Fetotoxicity: Fetal wts. No terata	Teratogenic NOEL

		25 mg/kg	No findings	Maternal toxicity NOEL Fetotoxicity NOEL
p-Nitroaniline PNA CAS No. 100-01-6	Rabbit Teratogenicity-Gavage 18/group	125 mg/kg 75 mg/kg 25 mg/kg	Maternal Toxicity: Deaths (7/18) Physical changes Maternal toxicity: Physical changes No findings	NOEL for Terata, fetotoxicity, and embryotoxicity NOAEL for Maternal Toxicity Unequivocal NOEL for Maternal Toxicity
p-Nitroaniline PNA CAS No. 100-01-6	Two-generation Rat Gavage Reproduction Study 15 males/30 females per group in F0 and F1 generations	9 mg/kg 2.5 mg/kg 0.25 mg/kg	F0/F1: all mating indices judged normal No findings No findings	NOEL for all reproductive endpoints

In summary, as seen previously in sections dealing with acute and repeated dose testing for mammalian toxicity endpoints, PNA has proven to produce the more significant comparative toxicity, hence the lower dosages used in the developmental toxicity studies listed (Nair et al, 1985). Albeit tested at lower dosages, only PNA exhibited significant developmental toxicity in the comparative rat studies. Severe maternal toxicity, along with embryotoxicity, fetotoxicity and frank malformations were observed at the highest dosage tested. Both maternal toxicity and fetotoxicity were observed at the mid dosage employed while the low dose selected was without treatment-related effect. As developmental effects were noted only at a dosage that produced significant maternal toxicity, PNA is not considered to cause a primary effect on fetal development.

PNA was found to be more toxic to rabbits than rats when tested in a rabbit developmental toxicity study (Nair et al, 1985). Frank maternal toxicity, including deaths, was observed at the highest dose tested, but there was no evidence of developmental toxicity observed, even at this test level.

ONA, on the other hand, produced substantive maternal toxicity in rats at the high dose tested, but produced no evidence of either embryotoxicity or fetotoxicity even at this level. Based on the study findings of a single malformation observed from two separate litters in the high dose group, it is unclear as to whether this was a treatment-related finding. The absence of production of this lesion in the previously discussed rat teratology study with PNA supports the conclusion that this was a spurious finding unrelated to ONA treatment.

PNA produced no evidence of adverse reproductive performance, including mating, fertility and pregnancy, littering or pup survival and development, in a Two-Generation rat Reproduction study using a top dosage which produced significant maternal toxicity (increased spleen weight, anemia, elevated blood methemoglobin levels) related to methemoglobinia following chronic dosing (Nair et al, 1990).

Based on the results of these studies and the NOEL's derived, an adequate margin of safety exists at the recommended occupational exposure limits established for each of these Mononitroanilines.

VI. REFERENCES

ACGIH. American Conference of Governmental Industrial Hygienists. 2001. *Documentation of the Threshold Limit Values & Biological Exposure Indices. 7th Edition.* Cincinnati, Ohio.

Barbee, SJ, JB Terrill, DJ De Sousa and CC Conaway. 1984. Subchronic inhalation toxicology of ethylene glycol monoethyl ether in the rat and rabbit. Environ. Health Perspect. 57:157-163.

Beard, RR, and Noe, JT. 1982. In *Patty's Industrial Hygiene and Toxicology,* Vol. IIA, Clayton, GD. And Clayton, FE., eds. Third revised ed. pp. 2415-2442.. Wiley-Interscience, New York.

EPIWIN, 2002. Version 3.10, Syracuse Research Corporation, Syracuse, New York.

European Chemical Bureau (ECB). 2000. IUCLID Dossier for o-Nitroaniline.

European Chemical Bureau (ECB). 2000. IUCLID Dossier for p-Nitroaniline.

Hardin, BD., Schuler, RL., Burg, JR., Booth, GM., Hazelden, KP., MacKenzie, KM., Piccirillo, VJ., and Smith, KN. 1987. Evaluation of 60 chemicals in a preliminary developmental toxicity test. Teratogen. Carcinogen. Mutagen. 7:29-48.

Hazardous Substances Data Bank (HSDB) – o-Nitroaniline, 2002

Hazardous Substances Data Bank (HSDB) – p-Nitroaniline, 2002

Klimisch, HJ., Andreae, M. and Tillman, U. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. J. Regulat. Toxicol. Pharmacol. 25:1-5.

Komsta, E., Secours, VE, Chu, I, Valli, VE, Morris, R, Harrison, J, Baranowski, E, Villeneuve, DC. 1989. Short-term toxicity of nine industrial chemicals. Bull. Environ. Contam. & Tox. 43:87-94

Linch, AL. 1974. Biological monitoring for industrial exposure to cyanogenic aromatic nitro and amino compounds. Amer. Indus. Hyg. Assoc. J. 35:426-432.

Lyman, WJ, Reehl, WF and Rosenblatt, DH. 1990. *Handbook of Chemical Property Estimation Methods. Environmental Behaviour of Organic Compounds*. American Chemical Society, Washington, DC.

Meylan, WM and Howard, PH. 1993. Environ. Toxicol. Chem. 26:2293-9.

Nair, RS, Auletta, CS, Schroeder, RE and Johannsen, FR. 1990. Chronic toxicity, oncogenic potential, and reproductive toxicity of p-Nitroaniline in rats. Fund. Appld. Toxicol. 15:607-621.

Nair, RS, Johannsen, FR. and Schroeder, RE. 1985. Evaluation of teratogenic potential of para-nitroaniline and para-nitrochlorobenzene in rats and rabbits. In *Toxicology of Nitroaromatic Compounds* (Rickert, DE. Ed) pp. 61-85. Hemisphere Publishing Corporation, New York. Also: Bio/dynamics, Inc. 1980. A teratogenicity study with p-Nitroaniline in rats. Solutia study No. BD-79-326.[EPA Documentation No. 878211846, Fiche No. OTS0206222] and Bio/dynamics, Inc. 1982. A teratogenicity study in rabbits with p-Nitroaniline. Solutia study No. BD-80-529. [EPA Document No. 878211841, Fiche No. OTS0206222]

OECD, 2002. Organization of Economic Cooperation and Development Existing Chemicals Programme, SIDS Dossier on the HPV Chemical (latest draft-May, 2002).

US EPA, 1998. Guidance for meeting the SIDS requirements (The SIDS Guide). Guidance for the HPV Challenge Program (11/31/98).

US EPA, 1999a. Determining the adequacy of existing data. Guidance for the HPV Challenge Program (2/10/99).

US EPA, 1999b. The use of structure-activity relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.

USEPA. 1999c. Development of Chemical Categories in the HPV Challenge Program.

Watanabe, T, Ishihara, N., Ikeda, M. 1976. Toxicity of and biological monitoring of 1,3-diamino-2,4,6-trinitrobenzene and other nitro-amino derivatives of benzene and chlorobenzene. Int. Arch. Occup. Environ. Health 37:157-168.

VII. ROBUST STUDY SUMMARIES
Appended

I U C L I D

Data Set

Existing Chemical	:	ID: 88-74-4
CAS No.	:	88-74-4
EINECS Name	:	2-nitroaniline
EINECS No.	:	201-855-4
TSCA Name	:	Benzenamine, 2-nitro-
Molecular Formula	:	C6H6N2O2

Producer Related Part

Company	:	Solutia Inc.
Creation date	:	04.04.2002

Substance Related Part

Company	:	Solutia Inc.
Creation date	:	04.04.2002
Memo	:	
Printing date	:	07.11.2002
Revision date	:	
Date of last Update	:	07.11.2002
Number of Pages	:	43
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 OECD AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE

1.0.3 IDENTITY OF RECIPIENTS

1.1 GENERAL SUBSTANCE INFORMATION

1.1.0 DETAILS ON TEMPLATE

1.1.1 SPECTRA

1.2 SYNONYMS

1.3 IMPURITIES

1.4 ADDITIVES

1.5 QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.7 USE PATTERN

1.7.1 TECHNOLOGY PRODUCTION/USE

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.9 SOURCE OF EXPOSURE

1.10.1 RECOMMENDATIONS/PRECAUTIONARY MEASURES

1.10.2 EMERGENCY MEASURES

1.11 PACKAGING

1.12 POSSIB. OF RENDERING SUBST. HARMLESS

1.13 STATEMENTS CONCERNING WASTE

1.14.1 WATER POLLUTION

1.14.2 MAJOR ACCIDENT HAZARDS

1.14.3 AIR POLLUTION

1.15 ADDITIONAL REMARKS

1.16 LAST LITERATURE SEARCH

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

2.1 MELTING POINT

Value	:	= 71.5 ° C
Sublimation	:	
Method	:	other
Year	:	1989
GLP	:	no data
Test substance	:	no data
Test substance	:	Technical grade ONA had purtiy of > 99% and was likely the source used.
Reliability	:	(2) valid with restrictions Listed as Peer Reviewed reference in Hazardous Substances Data Bank (2002) for 2-nitroaniline.
Flag	:	Critical study for SIDS endpoint

24.10.2002 (4)

2.2 BOILING POINT

Value	:	= 284 ° C at
Decomposition	:	
Method	:	other
Year	:	1989
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions Listed as Peer Reviewed reference in Hazardous Substances Data Bank (2002) for 2-nitroaniline.
Flag	:	Critical study for SIDS endpoint

24.10.2002 (4)

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	= .0368 hPa at 25° C
Decomposition	:	
Method		other (calculated)
Year	:	1989
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions Cited as Peer Reviewed reference in Hazardous Substances Data Bank (2002) for 2-nitroaniline.
Flag	:	Critical study for SIDS endpoint

24.10.2002 (5)

2.5 PARTITION COEFFICIENT

Log pow	:	1.85 at ° C
Method		other (calculated)

Year	:	1985
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions Listed as Peer Reviewed reference in Hazardous Substances Data Bank (2002) for 2-nitroaniline and listed as Recommended value in SRC CHEMFATE data base (2002).
Flag	:	Critical study for SIDS endpoint

24.10.2002 (8)

2.6.1 WATER SOLUBILITY

Value	:	= 1470 mg/l at 25 ° C
Qualitative	:	
Pka	:	at 25 ° C
PH	:	at and ° C
Method	:	other
Year	:	1991
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions Listed as Peer Reviewed reference in Hazardous Substances Data Bank (2002) for 2-nitroaniline and SRC CHEMFATE Data base (2002).
Flag	:	Critical study for SIDS endpoint

24.10.2002 (18)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	other
Light spect.	:	> 290 nm
Rel. intensity	:	based on Intensity of Sunlight
Direct photolysis		
Halflife t1/2	:	= 9.5 hour(s)
Degradation	:	= 16 % after 3 hour(s)
Quantum yield	:	
Indirect photolysis		
Sensitizer	:	OH
Conc. of sens.	:	
Rate constant	:	= .000000000013 cm3/(molecule*sec)
Degradation	:	% after
Deg. Product	:	
Method	:	other (calculated)
Year	:	2002
GLP	:	no
Test substance	:	no data
Method	:	Direct photodegradation measured using a medium-pressure mercury arc emitting > 290 mu; irridiations were conducted in triethylamine for 3 hrs; Additionally, a calculated value of 9.5 hr was derived by AOP Computer program v1.90. The program estimates the Atmospheric Oxidation Potential by estimating the rate constant for the atmosphere, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. The methodology is based on the SAR methods developed by Atkinson et al, 1987, Intern. J. Chem. Kinet. 19: 799-828 and described by Meylan and Howard, 1993, Chemosphere 26:2293-2299.
Reliability	:	(2) valid with restrictions Measurements published in a peer reviewed journal. Estimated value based on model recommended by US EPA.
Flag	:	Critical study for SIDS endpoint

25.10.2002 (1)

3.1.2 STABILITY IN WATER

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	other
Air (level I)	:	.525
Water (level I)	:	36.1
Soil (level I)	:	63.2
Biota (level II / III)	:	
Soil (level II / III)	:	.111
Method	:	other
Year	:	2002
Method	:	Estimation using measured values from reference documents were possible and incorporated into EPIWIN from Syracuse Research Corp and

possible and incorporated into EPIWIN from Syracuse Research Corp and based on Meylan, 1993 methodology as adopted by Mackay et al 1996. Second Soil entry includes data in Sediments.Values employed were: Mol wt=138.13; Gebrt;s KC=5.9e-008 atm-m3/mole (Henry database); Vapor Press=0.00277 mm Hg (user entry); Log Kow=1.85 (user entry); Soil Koc-29 (calc by model). Emissions rates for each of the three compartments (air, soil and water) were 1000 kg/hr.

Results

```
Chem Name    : o-Nitroaniline
  Molecular Wt: 138.13
  Henry's LC  : 5.9e-008 atm-m3/mole (Henry database)
  Vapor Press : 0.00277 mm Hg  (user-entered)
  Log Kow     : 1.85  (user-entered)
  Soil Koc    : 29  (calc by model)

          Concentration   Half-Life    Emissions
            (percent)        (hr)       (kg/hr)
   Air       0.525           19.1         1000
   Water     36.1            900          1000
   Soil      63.2            900          1000
   Sediment  0.111           3.6e+003     0

             Fugacity    Reaction    Advection   Reaction
Advection
              (atm)      (kg/hr)      (kg/hr)    (percent)
(percent)
   Air       2.03e-011    418         115         13.9
3.84
   Water     1.69e-012    609         791         20.3
26.4
   Soil      3.3e-011     1.07e+003   0           35.6
0
   Sediment  1.53e-012    0.469       0.0487      0.0156
0.00162

   Persistence Time: 730 hr
   Reaction Time:    1.05e+003 hr
   Advection Time:   2.42e+003 hr
   Percent Reacted:  69.8
   Percent Advected: 30.2

   Half-Lives (hr), (based upon Biowin (Ultimate), several
screening studies
   showing poor biodegradation and Aopwin):
      Air:      19.08
      Water:    900
      Soil:     900
      Sediment: 3600
        Biowin estimate: 2.589  (weeks-months)

   Advection Times (hr):
      Air:      100
      Water:    1000
      Sediment: 5e+004
```

Reliability : (2) valid with restrictions
Estimated values based on model recommended by US EPA.

Flag : Critical study for SIDS endpoint
24.10.2002 (6)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	
Concentration	:	5mg/l related to Test substance related to
Contact time	:	24 hour(s)
Degradation	:	= 7 % after 10 month
Result	:	under test conditions no biodegradation observed
Deg. Product	:	
Method	:	other
Year	:	1975
GLP	:	no
Test substance	:	other TS
Method	:	Semi-continuous activated sludge (SCAS) test was carried out over a 10-month period at a final addition rate of 5 mg ONA per 24-hr cycle. The methodology used was a standard procedure published in JAOCS 42:986 (1965) and used the modified feed techniques as described in JAOCS 46:432 (1969). ONA concentration was determined using UV spectrophotometry after extraction of the sludge with methylene chloride. Analysis was performed on one 24-hr cycle per week. Activated sludge obtained from local waste treatment facility.
Result	:	No significant biodegradation occurred, as a mean (+/-95% CI) loss was 7 (+/-11) %. No evidence of any inhibition of the normal sludge growth rate was observed.
Test substance	:	Used Technical grade ONA with purity > 99%.
Reliability	:	(2) valid with restrictions Study was conducted prior to codification of GLPs but is considered well documented. The methodology used in this study has now been codified into internationally accepted test guidance for biodegradability determination.
Flag	:	Critical study for SIDS endpoint

24.10.2002 (16)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	semistatic
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
LC50	:	= 19.5
Method	:	Directive 84/449/EEC, C.1 "Acute toxicity for fish"
Year	:	1991
GLP	:	no data
Test substance	:	other TS
Method	:	96 hr acute toxicity test was conducted in a semistatic system according to the OECD Guideline 202, as published in 1984. Zebrafish were approx. 3 mo. of age and weighed between 200-350 mg; both sexes were used. Fish were not fed 24h prior to testing and during the 96-h exposure period. A 12-h light;dark cycle was employed. The test water was charcoal-filtered, aerated tap water which was mixed with a stock solution of the chemical in distilled water and stirred at room temperature. The pH, dissolved oxygen and temperature of the water were 8.6+/-0.3, 85+/_15% and 26.5+/-1 degree C., respectively. Once a day the concentrations were checked photometrically and the test solutions were renewed if required. LC50 values were calculated using a computer program based on the method of Litchfield and Wilcoxon (1949).
Result	:	The 96 hr LC50 was determined to be 19.5 mg/l with SE of +/- 1.7 mg/L.
Test substance	:	Test sample purchased from a chemical supplier; Technical grade was typically > 99%.
Reliability	:	(1) valid without restriction No information was reported in the article about conduct under GLPs; however, as this study was conducted specifically to meet OECD test guideline 202 it is reasonable to assume that it was conducted under GLPs as well.
Flag	:	Critical study for SIDS endpoint

16.10.2002 (19)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	
NOEC	:	>= 12.5
EC50	:	= 14.5
Method	:	EPA OTS 797.1300
Year	:	1983
GLP	:	yes
Test substance	:	other TS
Method	:	Test article dissolved in Dimethyl Formamide (0.5 ml/L) and introduced to glass jars filled with well water; DO, pH, alkalinity and hardness measured prior to and after testing. Three replicates run, using 10 Daphnia per dosage level per rep. Dosages evaluated: control, solvent control, 6.25, 12.5, 25, 50 and 100 mg/L.
Result	:	EC50 values (95% CI) of 18.7 (12.5 -25) mg/L at 24 hr and 14.5 (12.5-25) mg/L. at 48-hr interval. The NOEC was 12.5 mg/L. Following was the % deaths observed: At 24 hr- Control (0%), solvent control (0 %), 6.25 mg/L (0 %), 12.5 (0 %), 25 (0 %), 50 (93.3%) and 100 mg/L (100%); At 48 hr -

Control (0%), solvent control (0%), 6.25 mg/L (0 %), 12.5 (30%), 25, (100%), 50 (100%), and 100 mg/L (100%). pH and dissolved oxygen ranged from 7.0-8.4 and 7.8-9.3 mg/L, respectively. The mean temp. was 23.7 degrees C. Alkalinity ranged between 298-400 mg/L and water hardness ranged between 220-370 mg/L. Evidence of insolubility of test substance was seen at 100 mg/L.

Test substance : Used Technical grade ONA, with purity of > 99%.
Reliability : (1) valid without restriction Study conducted according to ASTM/EPA guidance, which is consistent with OECD test guidance.
Flag : Critical study for SIDS endpoint
16.10.2002 (15)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : Scenedesmus sp. (Algae)
Endpoint : growth rate
Exposure period : 48 hour(s)
Unit : mg/l
Analytical monitoring : no data
EC50 : = 64.5
Method : OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year : 2001
GLP : no data
Test substance : other TS
Method : A 48-hr algae inhibition test following OECD test methods was conducted using S. obliquus as the test organism. Five concentration gradients were used, in concentration spacing of 0.2. pH of the culture medium was adjusted to 7.2+/-0.2. Two replicates of each concentration and untreated control were run. The algae in the logarithmic growing period were inoculated into 250 ml Erlenmeyer flasks, and added to 60 ml of the culture media, compound and algae. The initial algae cell concentration was approx. 1 x 10E4 cells/ml. The culture was incubated under a continuous light by fluorescent bulb at 20+/-1 degree C and average illumination intensity of 4000 lux. Growth was monitored by electron microscope (400X). EC values were determined by one variable linear regression analysis.
Test substance : Test sample purchased from chemical supplier; typical technical grade purity of ONA was 99%.
Reliability : (1) valid without restriction
No mention made regarding conduct under GLPs in article; however, as this study was conducted specifically to meet OECD guideline 201 it can reasonably be assumed that it also was conducted under GLPs.
Flag : Critical study for SIDS endpoint
27.08.2002 (7)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	20
Vehicle	:	other
Value	:	= 2050 mg/kg bw
Method	:	other
Year	:	1977
GLP	:	no
Test substance	:	other TS
Method	:	calc. method of deBeer, 1945, J. Pharmacol. Experimen. Ther. 85:1. Test substance was Technical grade ONA with purity of > 99%; administered as 10% corn oil solution Used 5 rats (mixed sex) /group. Four groups of rats were administered test article by gavage in increasing doses at increments of 0.1 fractional log intervals. Clinical signs recorded daily and body wts. recorded weekly. Animals observed for 14 days. Necropsies were performed on all animals. Food and water given ad libitum; humidity and temp. controlled.
Result	:	OLD50=2050 mg/kg; 95% CI of 1760-2380; all deaths occurred within 24 hrs.; Deaths: 1260-0/5; 1580-1/5, 2000-2/5, 2510-5/5; Signs of toxicity: yellow colored urine, generalized weakness; Observations at autopsy for decedents-hemorrhagic lungs, liver hyperemia, abdominal cavity yellow stained, g.i. irritation; for survivors - viscera appeared normal.
Reliability	:	(2) valid with restrictions Conducted using fewer animals than # 401; conduct consistent with but prior to enactment of GLP guidelines; This was a supplemental study to the HPV program in that an acute study by another route has been used to fullfill this HPV data endpoint.

07.11.2002 (17)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC0
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	10
Vehicle	:	other
Exposure time	:	4 hour(s)
Value	:	> 2529 mg/m³
Method	:	OECD Guide-line 403 "Acute Inhalation Toxicity"
Year	:	1996
GLP	:	yes
Test substance	:	other TS
Method	:	Test article used was 65% aqueous solution of Technical grade ONA (typical purity of 99%). Groups of 5 male and 5 female rats were exposed to a single aerosol concentration of ONA solution in PEG (to facilitate nebulization) under nose only conditions; the chamber was operated under dynamic exposure conditions. Animals were observed daily for clinical signs; body wts recorded on days 3, 7 and 14. Clinical observations were consistent with a Functional Observational Battery set of indices; methemoglobin determinations were made following exposure. All rats underwent a gross necropsy at study term. Food and water were given ad libitum. Observation period was 14 days. A vehicle control group of rats

		was exposed similarly to polyethylene glycol/acetone. Analytical test levels determined by GC method; particle size determined using cascade impactor. Statistical evaluations performed on body weights and physiological data using ANOVA procedures.
Result	:	Limit test No deaths occurred at the maximum achievable level tested of 2,529 mg/m3 (analytical level); the MMAD was 2.1 um indicating particle sizes of a respirable range. Animals exposed at this level exhibited decrements in body weight gain, hypothermia, distinct discoloration of the urine, and bradypnea, all of which were attributed to test article. These observations persisted no longer than 1 day following exposure. No adverse effects were noted in reflex measurements. No macroscopic findings attributable to test article were observed.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

26.08.2002 (2)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD0
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male/female
Number of animals	:	3
Vehicle	:	other
Value	:	> 7940 mg/kg bw
Method	:	other
Year	:	1977
GLP	:	no
Test substance	:	other TS
Method	:	Determination of Minimum Lethal Dose, thus used 1-2 animals /group; 24-hr occlusive dermal patch with 14-day observation period; necropsy at sacrifice, daily cage-side observations made for 2 weeks and weights recorded initially and after 7 and 14 days. Test article used was Technical grade ONA with purity > 99%; Administered as 40% solution-suspension in corn oil. Administered to clipped, intact skin of rabbits for 24-hr exposure under occluded conditions. Then removed and animals observed for 14 days.
Result	:	No deaths (0/1) at 5010 mg/kg or (0/2) at 7940 mg/kg; Observations: Yellow staining, reduced appetite and activity during first 3 days; all normal on day 14. No macroscopic necropsy findings.
Conclusion	:	Considered sufficient to establish toxicity to rodents by dermal route
Reliability	:	(2) valid with restrictions Used a small no. animals; conducted consistent with but prior to enactment of US GLPs in 1979; this study was a Supplemental study to the HPV program since another study by a another route was chosed to fullfill this HPV Endpoint.

07.11.2002 (17)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Species	:	rat
Sex	:	male
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation
Exposure period	:	6 hr/day
Frequency of treatment	:	5 days/week for 4 weeks
Post obs. period	:	none
Doses	:	9.8 and 93 mg/m3 (analytically determined conc.)
Control group	:	yes, concurrent no treatment
NOAEL	:	= 9.8 mg/m³
LOAEL	:	= 93 mg/m³
Method	:	OECD Guide-line 412 "Repeated Dose Inhalation Toxicity: 28-day or 14-day Study"
Year	:	1983
GLP	:	yes
Test substance	:	other TS
Method	:	Test material used was Technical grade ONA with purity > 99%. Test article generation used preheated nitrogen which was passed over the test agent in a paraffin oil bath; thus, no solvent, like CELLOSOLV, as used in a previous 4-wk inhalation study (BD-81-322), was employed in this study. This study was designed to determine whether ONA alone induced testicular effects observed in study BD-81-322, using CELLOSOLV solvent; Thus, each test group consisted of 10 male rats; daily observations, hematology (HGB, HCT, RBC, MET, retic, clot time, RBC morph and t/diff. leukocytes) evaluated on all animals prior to sacrifice; Brain and testicular wts were recorded while testes and epididymides were examined grossly and microscopically for all test animals. Body weight, hematology data and absolute and relative organ weights were treated for statistical differences. Parametric analysis was performed using ANOVA methods followed by Dunnet's test when mean differences were observed between dose groups; Kruskal Wallis test and Dunn's rank sum test were used for nonparametric analysis. Both 5% and 1% levels of significance were reported for each parameter. Whole body exposure in stainless steel chamber; analytically determined doses were 9.8 and 93 mg/m3 respectively. Analysis done by UV 4x daily, particle size confirmed during week 1 and rechecked periodically using Cascade impactor.
Remark	:	This study confirms that ONA produces no effects on testes following inhalation exposure and that results of a previous study (BD-81-322) were the result of use of CELLOSOLV as vehicle. These results, in conjuction with findings in the previous study cited earlier, are sufficient to meet all toxicity parameters established in OECD test guideline 412.
Result	:	Mean testicular wts (absolute and relative) were comparable to controls in both ONA test groups; no gross or microscopic changes in testes/epididymides were observed; Minimal changes in some hematological parameters (increases in methemoglobin i.e. MET and HCT and decreased total leuk. and seg. neutrophils) were seen at 93 mg/m3
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

07.11.2002 (11)

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley

Route of admin.	:	inhalation
Exposure period	:	6 hrs/day
Frequency of treatment	:	5 days/week for 4 weeks
Post obs. period	:	none
Doses	:	10, 30 and 73 mg/m3
Control group	:	yes, concurrent vehicle
NOAEL	:	= 30 mg/m³
LOAEL	:	= 73 mg/m³
Method	:	OECD Guide-line 412 "Repeated Dose Inhalation Toxicity: 28-day or 14-day Study"
Year	:	1982
GLP	:	yes
Test substance	:	other TS
Method	:	Test substance used was Technical grade ONA with purity of > 99% which was mixed with 2000 mg/m3 CELLOSOLVE (ethylene glycol monoethyl ether) as a concurrent vehicle; 10 rats/sex/group were exposed in 1 cub. meter steel/glass chambers via whole body exposure; Analytically determined (4X/d) concentration means were: 10, 27.5 and 73 mg/m3, respectively. Particle size means were all below 1 micron for each aerosol concentration. All animals were obs erved daily for toxic signs, weighed weekly, and underwent examination for clinical chemistries, hematology, ocular toxicity. Organ weights were taken at necropsy and microscopic exams were conducted on over 40 tissues for all high dose and control animals and target organs for all animals. Body weights, food consumption, hematology and clinical chemistry, absolute and relative organ weights were analyzed using ANOVA methods followed by Dunnet's test for parametric parameters while nonparametric parameters were subjected to Kruskal Wallis test followed by Dunn's rank sum test to determine statistical differences. Both 5% and 1% levels of significance were reported for each parameter.
Remark	:	Ambiguous information on testicular effects were resolved with a follow up study (BD-82-270) which assessed the issue of testes effects and the confounding use of Cellosolv as the solvent in this study. Subsequent results confirmed cellosolv as the affective agent.
Result	:	Treatment-related effects : 73 mg/m3 - Statistically decreased leukocytes in males, and significantly reduced hbg and rbc in females, increased polychromia, anisocytosis and poikilocytosis in males and females, increased rel. liver wts for females (no correponding histo), decreased absolute and relative testes wts corresponding with degeneration of the germinal epithelium seen microscopically.
Conclusion	:	Study results involving effects on the testes are considered unreliable due to incorrect choice of vehicle control (CELLOSOLVE, which was determined to be a testicular toxin but only after this study was conducted). The issue was resolved after conduct of a follow up study (BD-82-270). However, results in this study confirm that ONA, even in combination with CELLOSOLVE, did not affect measured clinical chemistry parameters, ophthalmology, organ weights, and gross and histopathology of a full set of tissues and organs which were not measured again in the second study (BD-82-270). For this reason, those portions of this study which were indicative of no discernable effect of ONA treatment, can be considered reliable.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

16.10.2002 (10)

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	14 days

Frequency of treatment	:	daily gavage administration throughout test period
Post obs. period	:	none
Doses	:	0, 1, 19, or 100 mg/kg bw
Control group	:	yes, concurrent vehicle
NOAEL	:	>= 100 mg/kg bw
Method	:	other
Year	:	1989
GLP	:	no data
Test substance	:	no data
Method	:	Groups of 10 M/10 F rats administered test article in corn oil via gavage for 14 consecutive days. A comprehensive evaluation of biochemical, hematological and histopathological evaluations were made at study termination. All animals examined daily for clinical signs and body weights were recorded daily. All animals necropsied on d15 and weights recorded for the following organs: brain, heart, liver, kidney and spleen. Histopathological exams were conducted on approx. 30 tissues and organs, including the gonads. ANOV analyses and Duncan's Multiple Range test ($p<0.05$) used to determine group differences.
Result	:	No treatment related findings in hematology, clinical chemistries, clinical observations,body and organ weights or macro- or microscopic findings attributable to treatment
Reliability	:	(2) valid with restrictions This study was of insufficient duration to be used to meet HPV testing guidance. It study was provided as Supplemental information as the HPV requirement has been fullfilled with another Repeat Dose study.

07.11.2002 (9)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	S. typhimurium strains TA98, TA100, TA1535 and TA1537 w & w/o S9
Concentration	:	1.5, 3, 6, 7, 15, 30, 40, 150, 225, 450, 600, and 1500 ug/plate
Cycotoxic conc.	:	3000 ug/plate (no background lawn) using TA100; 1000 ug/plate tolerated w & w/o S9
Metabolic activation	:	with and without
Result	:	negative
Method	:	Other
Year	:	1978
GLP	:	no
Test substance	:	other TS
Method	:	Statistical test used: after data transformation - 1-sided t-test; $p<0.01$ Test material used was Technical grade ONA with purity of > 99%; Appropriate positive controls were employed to validate this test methodology.
Result	:	Negative response seen in spot test at maximum conc. of 10000 ug/plate with and without S9 No significant mutagenic activity seen in any of the 4 tester strains; all positive controls validated adequacy of method used.
Reliability	:	(2) valid with restrictions Study conducted consistent with but prior to development of US GLP's in 6/79 and OECD Test Guide 471; study results are confirmed in numerous other published articles.
Flag	:	Critical study for SIDS endpoint

07.11.2002 (12)

Type	:	Chromosomal aberration test
System of testing	:	CHO cells maintained in Eagle MEM media
Concentration	:	1 - 10 mM
Cycotoxic conc.	:	no information provided

Metabolic activation	:	with and without
Result	:	ambiguous
Method	:	other
Year	:	1994
GLP	:	no data
Test substance	:	other TS
Method	:	After overnight incubation in complete medium, the medium was replaced with either serum-free complete medium or an exogenous metabolic activation medium, each containing test material. Cells were treated for 1 h, followed by washing (3X) and incubated in complete medium for either 10h or 16 hr. Colcemid was added for the final 2h of incubation. 100 metaphase cells scored from each of 2 cultures for each treatment level. Negative control group was used. Positive controls included MMS and CP. Statistical package used was EPA's Chromosomal aberration assay data management and analysis system.
Remark	:	This study is Supplemental information as a fully acceptable micronucleus test has been used to fullfill this HPV endpoint.
Result	:	Test material induced a significant ($p<0.01$) increase in chromosomal aberrations measured 10h after pretreatment both in the presence and absence (1 of 2 trials) of S9. A statistically significant increase in aberrations was also detected after 16h, but only with S9. A dose-response trend was evident in all cases, but only strong responses were observed at the very highest (10 mM) dose tested. The primary aberration observed was a large isochromatid discontinuity seen only in the long arm of the X chromosome. Image enhancement revealed presence of material in the affected region and the alignment of the dislocated segment, making classification of this lesion uncertain. In a separate experiment, all X-chromosome isochromatid anomalies were screened to perform the analysis with and without discontinuity. When excluded, there was no increase in aberrations observed. The cause of this isochromatid discontinuity is uncertain.
Conclusion	:	The authors state that "It is not clear whether this phenomenon represents a legitimate chromosomal aberration."
Reliability	:	(3) invalid

07.11.2002 (3)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Micronucleus assay
Species	:	mouse
Sex	:	male/female
Strain	:	CD-1
Route of admin.	:	i.p.
Exposure period	:	Single doses given twice, 24 hrs apart
Doses	:	0, 50, 250, and 500 mg/kg
Result	:	negative
Method	:	OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year	:	1989
GLP	:	yes
Test substance	:	other TS
Method	:	Dosages administered in corn oil (10 ml/kg). In a preliminary study, the IP LD50 in mice was determined to be 723 mg/kg; further, the PCD/total erythrocyte ratio was evaluated to determine bone marrow cytotoxicity potential. After completion of dosing, bone marrow was taken from both femors and pooled for slide preparation. Slides were stained with Wright-Giemsa stain pak and scoring was conducted by 2 independent readers. The no. of micronuclear polychromatic erythrocytes (PCEs) per 1000 PCEs and the no. of PCEs and normochromatic erythrocytes/1000 erythrocytes were evaluated for each animal. The individual animal was used as the statistical unit and the Student's T (1-sided) test used to compare treatment

and control group means. A level of p <0.05 was used for all parameters to determine statistical significance.
Highest dosage used was approx. 70% of calc. IP LD50 of 730 mg/kg, as determined in intralaboratory range-find study with mice
Technical grade ONA with purity of > 99% used in this test.Cyclophos phamide (40 mg/kg) positive control used.

Result : No increases in micronuclei observed at any ONA dose level; positive control verified the method. Signs of listlessness and unresponsive behavior seen in both sexes at 500 and 250 mg/kg and females at 50 mg/kg ONA; statistically lower body weights observed in females at 500 mg/kg after 48 hr dosing.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

27.08.2002 (14)

Type : Micronucleus assay
Species : mouse
Sex : male/female
Strain : C57BL
Route of admin. : i.p.
Exposure period : Treated twice with 24 h between each treatment
Doses : 0, 246, 492 and 738 mg/kg
Result : ambiguous
Method : OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year : 1994
GLP : no data
Test substance : no data
Method : Test article administered IP in olive oil to groups of 5M and 5F mice; controls received only olive oil.High dose reportly was estimated to be 75% of LD50 as determined in a preliminary experiment. After 36 h following the second treament, mice were sacrificed and bone marrow removed, a cell suspension made and slides prepared. 500 polychromatic erythrocytes from each animal were scored for the presence of micronuclei. The ratio of PEs to normochromatic cells was also determined to assess cytotoxicity. Data were analyzed using EPA's micronucleus assay data management and analysis system (p<0.05)

Result : No statistically significant increase in PE ratios; thus, no indication of cytotoxicity. A small 1.2+/- 0.08 vs. 2.8+/- 1.50, but statistically (p<0.05) significant increase in micronuclei was observed at the highest dose tested of 738 mg/kg only in male mice. This effect was observed only in males, not females at this dose level; no effects were seen in either males or females at lower dose levels.

Reliability : (3) invalid
Considered ambiguous, as the effect noted was small, seen only at one dose level and observed in only one sex. Provided as Supplemental information.

07.11.2002 (3)

5.7 CARCINOGENITY

5.8 TOXICITY TO REPRODUCTION

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : rat
Sex : female
Strain : Sprague-Dawley

Route of admin.	:	gavage
Exposure period	:	Days 6-15 of gestation
Frequency of treatment	:	Daily throughout exposure period
Duration of test	:	Treated on gestation days 6-15, sacrificed on gestation day 21 for fetal exams
Doses	:	0, 100, 300, 600 mg/kg/day in corn oil
Control group	:	yes, concurrent vehicle
NOAEL Maternalt.	:	= 100 mg/kg bw
NOAEL Teratogen	:	= 600 mg/kg bw
NOAEL Embryotoxicity	:	= 600 mg/kg bw
NOAEL Fetotoxicity	:	= 600 - mg/kg bw
Method	:	OECD Guide-line 414 "Teratogenicity"
Year	:	1985
GLP	:	yes
Test substance	:	other TS
Method	:	25 pregnant females/group; daily gavage in corn oil at constant volume of 10 ml/kg/d from gestation days 6-15. Dosing solutions were analyzed (GC) for test material concentration and stability periodically throughout the study. Nidation data collected at sacrifice, live fetuses examined externally and by Wilson sections and skeletal exam techniques were used to detect any variations or abnormalities. Body weights and food consumption were collected on gestation days 0, 6, 10, 13, 16 and 21 (day of termination). Daily clinical signs of toxicity recorded on gestation days 6-21. Statistical methods used: body wts. analyzed using Dunnett's test; Counted data (corpora lutea, implants, resorption, live/dead pups) analyzed using Mann-whitney U test; response data (eg. pregnancy rates, litters with postimplantation loss, etc.) assessed with Fischer's exact test and Chi square test.
Result	:	Maternal toxicity evidenced by reduced body wt gain at 600 mg/kg and lower food consumption at 600 and 300 mg/kg; both indices were slightly (not stat. signif.) lower than controls, but not considered related to treatment as these events were observed in this group prior to treatment No effects on pregnancy rates, mean no. live and dead pups, resorptions, nidations, c. lutea; Mean fetal wts were slightly, but not statistically lower than control in 600 mg/kg group. No differences seen in no. litters, fetuses or malformations. One malformation (situs inversus syndrome) was seen in single fetuses from two litters at the 600 mg/kg level; this incidence and lack of correlation to similar findings associated with other mononitroanilines supports the conclusion that this was a spurious finding.
Test substance	:	Technical grade of ONA used with purity of > 99%.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

16.10.2002 (13)

04.04.2002

5.10 OTHER RELEVANT INFORMATION

5.11 EXPERIENCE WITH HUMAN EXPOSURE

(1) Barltrop, JA and Bunce, NJ. 1968. Organic photochemistry. Part VIII. The photochemical reduction of nitro-compounds. J. Chem. Soc. (C) 1968:1467-1474.

(2) Bayer Corp. 1996. Study on acute inhalation toxicity in rats according to OECD No. 403 by T. Martins. Bayer Study no. T3044113. [EPA Document No. 86960000565; Fiche no. OTS0558766]

(3) Blakey, DH, Maus, KL, Bell,R, Bayley, J, Douglas, GR, and Nestmann, ER. 1994. Mutation Research 320:273-283.

(4) Budavari, S. (ed.) 1989. The Merck Index- an encyclopedia of chemicals, drugs and biologicals. Whitehouse Station, NJ. p. 1042.

(5) Daubert, TE and Danner, RP, 1989. Physical and thermodynamic properties of pure chemicals data compilation. Taylor and Francis, Washington, DC.

(6) EPIWIN, Version, 2002. version 3.10. Syracuse Research Corp, Syracuse, NY.

(7) G.-H. Lu, Yuan, X, and Zhao, Y-H. 2001. Chemosphere 44:437-440

(8) Hansch, C and Leo, L, 1985. Medchem Project. Claremont, CA. Pomona College Issue 26.

(9) Komsta, E, Secours, VE, Chu, I, Valli, VE, Morris, R, Harrison, J, Baranowski, E and Villeneuve, DC. 1989. Bull. Environ. Contam.Toxicol. 43:87-94.

(10) Solutia study no. BD-81-322. Four week inhalation toxicity study of O-Nitroaniline in the rat. [EPA 878214205; Fiche no. OTS0206486]

(11) Solutia study no. BD-82-270. Four week inhalation study of Ortho-Nitroaniline in male rats [EPA Document no. 878214205; Fiche no. OTS0206486]

(12) Solutia study no. LF-78-144. Salmonella mutagenicity assay of O-Nitroaniline (Technical). [EPA Document no. 878211039; Fiche no. OTS0206222].

(13) Solutia study no. ML-82-89. Orthonitroaniline: A teratology study in rats. [EPA Document no. 868600002; Fiches no. OTS0510153]

(14) Solutia study no. ML-89-7. Micronucleus assay with o-nitroaniline.

(15) Solutia study no. MO1983X083. Acute toxicity of o-Nitroaniline for Daphnia magna.

(16) Solutia study no. MO20020140. Biodegradation testing of o-nitroaniline (ONA) and p-nitroaniline (PNA).

(17) Solutia study no. Y-76-438 Toxicological investigation: O-Nitroaniline [EPA Document No. 878211634; Fiche no. OTS0206222].

(18) Suzuki, T.1991. J. Computer-Aided Molecular Design 5:149-166.

(19) Zok, S, Goerge, G, Kalsch, W and Nagel, R. 1991. Sci. Total Environ. 109/110:411-421.

7.1 END POINT SUMMARY

7.2 HAZARD SUMMARY

7.3 RISK ASSESSMENT

I U C L I D

Data Set

Existing Chemical	:	ID: 100-01-6
CAS No.	:	100-01-6
EINECS Name	:	4-nitroaniline
EINECS No.	:	202-810-1
TSCA Name	:	Benzenamine, 4-nitro-
Molecular Formula	:	C6H6N2O2

Producer Related Part

Company	:	Solutia Inc.
Creation date	:	04.04.2002

Substance Related Part

Company	:	Solutia Inc.
Creation date	:	04.04.2002
Memo	:	
Printing date	:	07.11.2002
Revision date	:	
Date of last Update	:	07.11.2002
Number of Pages	:	43
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 OECD AND COMPANY INFORMATION

24.10.2002

1.0.2 LOCATION OF PRODUCTION SITE

1.0.3 IDENTITY OF RECIPIENTS

1.1 GENERAL SUBSTANCE INFORMATION

1.1.0 DETAILS ON TEMPLATE

1.1.1 SPECTRA

1.2 SYNONYMS

1.3 IMPURITIES

1.4 ADDITIVES

1.5 QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.7 USE PATTERN

1.7.1 TECHNOLOGY PRODUCTION/USE

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.9 SOURCE OF EXPOSURE

1.10.1 RECOMMENDATIONS/PRECAUTIONARY MEASURES

1.10.2 EMERGENCY MEASURES

1.11 PACKAGING

1.12 POSSIB. OF RENDERING SUBST. HARMLESS

1.13 STATEMENTS CONCERNING WASTE

1.14.1 WATER POLLUTION

1.14.2 MAJOR ACCIDENT HAZARDS

1.14.3 AIR POLLUTION

1.15 ADDITIONAL REMARKS

1.16 LAST LITERATURE SEARCH

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

2.1 MELTING POINT

Value	:	= 146 ° C
Sublimation	:	
Method	:	other
Year	:	1989
GLP	:	no data
Test substance	:	other TS
Reliability	:	(2) valid with restrictions Reference cited as Peer reviewed in Hazardous Substance Data Bank for p-Nitroaniline (2002) and as Recommended value in SRC CHEMFATE data base (2002).
Flag	:	Critical study for SIDS endpoint

07.11.2002 (1)

2.2 BOILING POINT

Value	:	= 332 ° C at
Decomposition	:	
Method	:	other
Year	:	1989
GLP	:	no data
Test substance	:	other TS
Reliability	:	(2) valid with restrictions Reference cited as Peer Reviewed in Hazardous Substances Data Band for p-Nitroaniline (2002) and cited as SRC Recommended value in CHEMFATE data base (2002)
Flag	:	Critical study for SIDS endpoint

07.11.2002 (1)

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	= .0053 hPa at 25° C
Decomposition	:	
Method		other (measured)
Year	:	1985
GLP	:	no data
Test substance	:	other TS
Reliability	:	(2) valid with restrictions Cited as peer reviewed reference in Hazardous Substances Data Bank for p-nitroaniline (2002).
Flag	:	Critical study for SIDS endpoint

24.10.2002 (3)

2.5 PARTITION COEFFICIENT

Log pow	:	= 1.39 at ° C

Method		other (calculated)
Year	:	1987
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions Recommended value in CHEMFATE data base (2002)
Flag	:	Critical study for SIDS endpoint

24.10.2002 (6)

2.6.1 WATER SOLUBILITY

Value	:	= 724 mg/l at 25 ° C
Qualitative	:	
Pka	:	at 25 ° C
PH	:	at and ° C
Method	:	other
Year	:	1991
GLP	:	no data
Test substance	:	other TS
Reliability	:	(2) valid with restrictions Cited as a Peer Reviewed reference in Hazardous Substance Data Bank for p-nitroaniline (2002).
Flag	:	Critical study for SIDS endpoint

24.10.2002 (19)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	other
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Indirect photolysis		
Sensitizer	:	OH
Conc. of sens.	:	
Rate constant	:	= .00000000001345366 cm3/(molecule*sec)
Degradation	:	= 50 % after 9.5 hour(s)
Deg. Product	:	not measured
Method	:	other (calculated)
Year	:	2002
GLP	:	no
Test substance	:	no data
Method	:	Calculated by AOP Computer Program, Vers. 1.90, Syracuse Research Corp. which estimates the Atmospheric Oxidation Potential. This program estimates the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. The model is based on SAR methods developed by Atkinson et al, 1987, Intern. J. Chem. Kinet. 19:799 and described in Meylan and Howard, 1993, Chemosphere 26: 2293-2299.
Reliability	:	(2) valid with restrictions Estimated value based on model recommended by EPA
Flag	:	Critical study for SIDS endpoint

24.10.2002 (4)

3.1.2 STABILITY IN WATER

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	other
Air (level I)	:	.588
Water (level I)	:	36.8
Soil (level I)	:	62.6
Biota (level II / III)	:	
Soil (level II / III)	:	.0138
Method	:	other
Year	:	2002
Method	:	Calculated according to Mackay, Level III. Assumed emissions (1000 kg/hr) to air, water and soil compartments using measured values as available from reference documents, including: Mol Wt=138.13; Henry's LC=1.26e-009 atm-me/mole (Henry database); Vapor Press=0.3 mm Hg (user entry); Log Kow=1.39 (user entry); Soil Koc=10.1 (calc by model). Last soil entry includes data estimate for sediments.
Results		`Chem Name : p-Nitroaniline` `Molecular Wt: 138.13`

```
  Henry's LC  : 1.26e-009 atm-m3/mole (Henry database)
  Vapor Press : 0.3 mm Hg  (user-entered)
  Log Kow     : 1.39  (user-entered)
  Soil Koc    : 10.1  (calc by model)

         Concentration   Half-Life    Emissions
           (percent)        (hr)       (kg/hr)
   Air       0.588           19          1000
   Water     36.8            20          1000
   Soil      62.6            20          1000
   Sediment  0.0138          60          0

             Fugacity    Reaction    Advection   Reaction
Advection
              (atm)      (kg/hr)      (kg/hr)    (percent)
(percent)
   Air       8.89e-013    18.3        5.02        0.611
0.167
   Water     1.44e-015    1.09e+003   31.5        36.4
1.05
   Soil      5.01e-014    1.85e+003   0           61.8
0
   Sediment  2.16e-016    0.136       0.000235    0.00453
7.84e-006

   Persistence Time: 28.5 hr
   Reaction Time:    28.9 hr
   Advection Time:   2.34e+003 hr
   Percent Reacted:  98.8
   Percent Advected: 1.22

   Half-Lives (hr), (based upon estimates from experimental
data):
      Air:      19
      Water:    20
      Soil:     20
      Sediment: 60

   Advection Times (hr):
      Air:      100
      Water:    1000
      Sediment: 5e+004
```

Reliability : (2) valid with restrictions
Estimated values based on model recommended by EPA.
Flag : Critical study for SIDS endpoint
24.10.2002 (4)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum :
Concentration : 5mg/l related to Test substance
related to
Contact time : 24 hour(s)
Degradation : = 82 % after 24 hour(s)

Result	:	other
Deg. Product	:	
Method	:	other
Year	:	1975
GLP	:	no
Test substance	:	other TS
Method	:	Semi-continuous activated sludge (SCAS) testing was carried out over a 10-month period at an addition rate of 5 mg per 24-hr cycle. The standardized test method used was published in JAOCS 42:986 (1965) and used the modified feed technique (JAOCS 46:432, 1969). Sludge was obtained from a local waste disposal site. Disappearance was measured after one 24-hr cycle per week using UV spectrophotometry to analyze the methylene chloride extract of the mixed liquor samples taken at that time.
Result	:	PNA appeared to be moderately degradable under these test conditions; however, the data obtained were somewhat erratic. During the 16th through 30th week of feeding, the degradation varied from moderately rapid to rapid with a mean rate and 95% confidence limits of 82+/-12%. During the last two months of testing, far lower rates (mean of 19.4+/-10%) were observed. These data seem to indicate a threshold toxic or inhibiting effect of PNA. Substantial inhibition of the normal sludge growth rate was observed.
Test substance	:	Technical grade PNA with purity > 99%.
Reliability	:	(2) valid with restrictions Study conducted prior to codification of GLPs but considered well documented. Methodology used has subsequently been incorporated into a standardized international test guideline for this study type.
Flag	:	Critical study for SIDS endpoint

07.11.2002 (16)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Salmo gairdneri (Fish, estuary, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
NOEC	:	= 10
LC50	:	= 45
Method	:	other
Year	:	1980
GLP	:	yes
Test substance	:	other TS
Method	:	Followed study design adopted by US EPA Committee on Methods for Toxicity Tests with Aquatic Organisms, 1975; design consistent with OECD 203. Groups of 10 fingerling (mean wt of 0.83 g/fish and length of 38 mm) were exposed to varying test concentrations in 15 liter of soft reconstituted water with a dissolved oxygen level of 8.6 mg/l, a pH of 7.4, total hardness of 45 mg/L CaCO3 and total alkalinity of 35 mg/l CaCO3. These vessels were kept in a water bath at 12 degrees C. Fish acclimated to the dilution were held without food for 48 hours prior to testing. Based on preliminary testing, each group of fish was exposed to one of six test concentrations ranging in a logarithmic series from 5.6 to 100 mg/L. Fish were added to the test chambers within 30 min. of the addition of the test article. Test concentrations were prepared in acetone (0.5 ml), based on total compound as the test article was > 99% pure and the dose solution was then added to each respective test chamber. Mortality rates, fish behavior and water quality data (temp, pH, ammonia levels) were monitored after 24, 48 and 96 hrs of treatment. Antimycin A was similarly tested as a concurrent positive control. Calculation of the LD50 and confidence limits was performed using a computerized program developed by Stephan, Busch, Smith, Burke and Andrew, 1978 from the US EPA Duluth, Minn Aquatic Laboratory.
Result	:	LC50 and (Confidence Limits): 96-hr=46(32-56) mg/L; 48-hr= 45 (32-56) mg/L; 24-hr = 47 (32-100) mg/L. No deaths were seen at any test concentration up to 32 mg/l through 96 hrs of testing. At 56 mg/l, mortality reached 80% after 24 hrs and 90% after 48 and at 96 hrs. 100% mortality occurred at all three time points at 100 mg/l. A yellow precipitate was observed at all test levels. Dissolved oxygen concentration ranged between 60-100% saturation and was considered adequate for testing. The pH values remained consistent throughout the test and the ammonia concentrations were below the toxic limit. The positive control responded as expected.
Test substance	:	Technical grade PNA with purity > 99%.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

15.10.2002 (9)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
NOEC	:	= 10
EC50	:	= 20

Method	:	other
Year	:	1980
GLP	:	yes
Test substance	:	other TS
Method	:	Followed study design outlined by the US EPA Committee on Methods for Toxicity Tests with Aquatic Organisms, 1975, and consistent with OECD Guideline # 202.The study was conducted in 250 ml glass beakers containing 200 ml well water with specified chemical characteristics and kept at 20 degrees C. The photoperiod was controlled to give 16 hr daylight. After an inital range-find study, groups of 10 D. magna (first instar less than 24 hr old) were added to one of 5 beakers containing a range of test material between 3.2 and 32 mg/L, spaced logarithmically. The test article was originally prepared in 0.5 mL acetone solutions (0.5 ml) prior to charging the beakers. Each concentration was run in duplicate. Fish mortality and behavior and water quality parameters (dissolved oxygen levels, pH and temperature) were measured at the beginning of the test and after 24 hr (mortality and behavior only) and 48 hrs. Predicted LC50 values and 95% confidence limits were calculated using the computerized program developed by Stephan, Busch, Smith, Burke and Andrew, 1978 from the US EPA Duluth, Minn Aquatic Laboratory.
Result	:	48 hr LC50 (CI) =20 (18-23) mg/L. All water quality parameters (20-12 deg. C; 8.8-9,0 mg/L DO, pH of 8.1-7.9 and water hardness of 255 ppm CaCO3) were found to be acceptable.
Test substance	:	Technical grade PNA with purity > 99%.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

15.10.2002 (10)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus sp. (Algae)
Endpoint	:	growth rate
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no data
EC50	:	= 54.9
Method	:	OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year	:	2001
GLP	:	no data
Test substance	:	other TS
Method	:	48-hr algae growth inhibition test following OECD guideline 201. Organism used was S. obliquus. pH of the culture medium was adjusted to 7.2+/-0.2. Five concentrations were used at log intervals of 0.2. Two replicates of each concentration plus a negative control were tested. The algae in the logarithmic growing period were inoculated into 250 ml Erlenmeyer flasks containing approx 60 ml of media, test article and algae. The initial algae cell concentration was 1x10E4 cells/ml. The culture was incubated under a continuous light at 20+/-1 degrees C while flourescent lamp and the average illumination intensity was about 4000 lux. Growth was monitored by an electron microscope (400X). The EC value was determined using a one variable linear regression analysis.
Test substance	:	Test material purchased from chemical supplier; typical technical grade purity of PNA was 99%.
Reliability	:	(1) valid without restriction No mention was made regarding conduct under GLPs in the literature article; however, as this study was conducted specifically to meet OECD Guideline 201, it can reasonably be assumed that it also was conducted under GLPs.
Flag	:	Critical study for SIDS endpoint

07.11.2002 (7)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	25
Vehicle	:	other
Value	:	= 1400 mg/kg bw
Method	:	other
Year	:	1976
GLP	:	no
Test substance	:	other TS
Method	:	Consistent with # 401,but fewer animals, ie. 5 rats of mixed sex/group were given test article in 5 increasing doses at increments of 0.1 fractional log intervals; animals observed daily for 14 days for clinical signs and weighed weekly. Food and water provided ad libitum and temp./humidity controlled. Necropsies performed on all animals that died and on survivors after 14d. Technical grade PNA used, with purity > 99%. Administered as 20% solution-suspension in corn oil
Result	:	OLD50 = 1400 mg/kg; Confidence Limits of 1230-1590 mg/kg; used method of deBeer, J.Pharmacol. Experimen. Ther. 85:1; Deaths - mg/kg: 794 (0/5), 1000 (1/5), 1260 (1/5), 1580 (4/5), 2000 (5/5), occurred within 7 days of dosing; Signs of toxicity: ocular discharge, tremors and convulsions; necrospy (decedents) - hemorrhagic areas of lung, liver discoloration and gi inflammation; all survivors had normal vicera after 14 days observation
Conclusion	:	Sufficiently robust to provide degree of acute toxicity in rodents; numerous additional literature citations for this endpoint also available.
Reliability	:	(2) valid with restrictions Conducted prior to, but consistent with, US GLPs which were enacted 6/79. Results are consistent with data in ECB IUCLID -PNA, 2002 for this endpoint, which had 5 values between 920-3250 mg/kg and 1 value as low as 750 mg/kg.
Flag	:	Critical study for SIDS endpoint

07.11.2002 (17)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD0
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male/female
Number of animals	:	3
Vehicle	:	other
Value	:	> 7940 mg/kg bw
Method	:	other
Year	:	1976
GLP	:	no
Test substance	:	other TS
Method	:	Test article administered as 40% solution-suspension in corn oil; applied occluded for 24 hrs to intact, clipped skin of rabbits, animals observed clinically for 14 days. Body weights were recorded weekly; all animals were necropsied after d14. Food and water available ad libitum and temp./humidity was controlled.

temp./humidity was controlled.

Result	:	Determination of Minimum Lethal Dose: Two dosages tested, 5010 mg/kg (0/1 deaths) and 7940 mg/kg (0/2 deaths); no significant untoward toxic signs were observed during the study, all viscera normal at necropsy
Test substance	:	Used Technical grade PNA, with purity of > 99%.
Conclusion	:	Sufficiently robust study to evaluate the minimum lethal dose; as this dose proved to be of a low toxicity, there would appear to be no reason to test at higher levels to define an LD50 by this route.
Reliability	:	(2) valid with restrictions This is provided as supplemental information since an acute oral toxicity study has been used to fulfill this HPV endpoint. Small, but sufficient no. animals to characterize toxicity; study conducted prior to, but consistent with, US GLPs enacted in 6/79.

07.11.2002 (17)

04.04.2002

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	90 days
Frequency of treatment	:	daily consecutive
Post obs. period	:	none
Doses	:	0, 3, 10, 30 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL	:	< 3 mg/kg bw
LOAEL	:	= 3 mg/kg bw
Method	:	OECD Guide-line 408 "Subchronic Oral Toxicity - Rodent: 90-day Study"
Year	:	1981
GLP	:	yes
Test substance	:	other TS
Method	:	Corn oil vehicle used and dosing occurred at a constant volume of 0.2 ml/100 g bdy wt; 20 rats/sex/group used; Clinical signs recorded daily, individual body weights and food consumption measured weekly, serum chemistries (SGPT, SAP, BUN, T. Bili., GLU, T. Prot., K, Na), urinalysis (Prot, microscop. elements, pH, Spec. grav., blood, Glu, ketones, urobilinogen, vol.) and hematology parameters (Hgn, HCT, WBC, RBC, MCV, MCHC, retics, red cell fragility and methemoglobin) examined after 44 and 88 days. All animals necropsied at study term and organ weights (brain, adrenals, kidneys, liver, spleen, pituitary, testis) weighed. Histopathologic exams were conducted on approx. 40 tissues and organs from all high dose and control rats and the spleens of all lower dose rats. Specifically, gonads were examined for all HD and C animals. Statistical

		Specifically, gonads were examined for all HD and C animals. Statistical analysis performed using: Bartlett's test (p<0.01), ANOVA, Dunnets' test, Mann-whitney U with Bonferroni Inequality test, and Kolmogorov-Smiranov 1 tail test (all at p<0.05 and p<0.01)
Result	:	30 mg/kg: Pale appearance around ears, statistically significant increase in urinary urobilinogen and methemoglobin levels, statistical increases in RBC counts and hemoglobin levels of both sexes. All animals had discolored spleens at necropsy, statistically increased spleen weights and splenomegaly and microscopic evidence of excessive splenic hemosiderin. 10 mg/kg: Statistically increased methemoglobin and decreased RBC counts and hemoglobin conc. (females only), all animals had splenomegly, elevated splenic wts, discolored spleens and microscopic pathology associated with excessive hemosiderin; 3 mg/kg: statistically elevated methemoglobin (both sexes) and microscopic findings in spleen
Test substance	:	Used Technical grade PNA with purity > 99%.
Conclusion	:	No effects observed on gonads.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

28.08.2002 (14)

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation
Exposure period	:	6 hours per day, 5 days per week
Frequency of treatment	:	4 weeks
Post obs. period	:	none
Doses	:	0, 10, 32, 80 mg/m3 (analytical)
Control group	:	yes, concurrent vehicle
NOAEL	:	< 10 mg/m³
LOAEL	:	= 10 mg/m³
Method	:	OECD Guide-line 407 "Repeated Dose Oral Toxicity - Rodent: 28-day or 14-d Study"
Year	:	1984
GLP	:	yes
Test substance	:	other TS
Method	:	Aerosol derived by passing air over PNA dissolved in isopropanol and warmed. Groups of 10 rats/sex/group were housed in stainless steel and glass chamber and exposed under whole body conditions to one of three levels of test material. A vehicle control group was exposed to isopropanol in a similar fashion and treated similarly for evaluation. Chamber atmospheres and particle size were analytically determined. Dosing occurred 6h/d, 5d/wk for 4 consecutive weeks; animals were observed daily for clinical signs , weighed weekly, food and water given ad libitum , serum chemistry (BUN, SGPT, SAP, GLU, ALB, T.Protein, Glob., Na, K, P, Ca, Cl) and hematology (Hgb, HCT, RBC, Methem., clot time, T/Differ. Leuko, red cell morph) parameters collected on day 0 and 28. Ophthalmoscopic exams conducted on day 0 and 28. Organ weights (gonads, hrt, kid, lvr, lu, pit, spln, brain) recorded at termination; all animals necropsied at term; microscopic evaluation of approx. 40 tissues and organs (including gonads) for all high dose and control rats; spleens examined for all lower dose animals. Statistical methods used included: Bartlett's test (p<0.01), and ANOVA, Krusal-Wallis, Dunn's Summed rank test - all (p<0.05 and p<0.01)
Result	:	80 mg/m3:non-statistical decreases in hemoglobin and hematocrit seen in males and females, statistical increase in methemoglobin in males and females, higher incidence of polychromasia and anisocytosis (females only), statistically elevated absolute and relative spleen wts for both sexes, histopthological exams revealed elevated iron deposition within splenic macrophages, extramedullary hematopoiesis in spleen (male and female) and liver (females only); 32 mg/kg: non-statistical decrease in hemoglobin in males, statistically elevated methemoglobin in males and females, higher

in males, statistically elevated methemoglobin in males and females, higher incidence of polychromasia (both sexes) and anisocytosis (females only), relative spleen wts increased statistically (males only), histopathology - increased iron deposition and extramedullary hematopoiesis in both males and females; 10 mg/m3: non-significant elevation in blood methemoglobin, significant increases in mean spleen weight (both sexes), iron deposition and extramedullary hematopoiesis seen in spleens (both sexes)

Test substance : Technical grade PNA with purity > 99%.
Reliability : (1) valid without restriction
Supplemental HPV study since a fully acceptable Subchronic study (see earlier entry in this Section) fulfills the Repeated Dose HPV Endpoint.

07.11.2002 (8)

05.04.2002

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : S. thyphimurium test strains TA98, TA100, TA1535, TA1537 w & w/o S9
Concentration : 0.01, 0.04, 0.2, 1, 1.5, 3, 4, 5, and 10 mg/plate
Cycotoxic conc. : no significant microbial toxicity observed up to 10 mg/plate with TA100
Metabolic activation : with and without
Result : positive
Method : OECD Guide-line 471 "Genetic Toxicology: Salmonella thyphimurium Reverse Mutation Assay"
Year : 1980
GLP : yes
Test substance : other TS
Method : Conducted both Spot test and Plate Incorporation Assay. Used DMSO as solvent, S9 was commerically available rat and mouse liver preparations. Appropriate positive (2-AA, 9-AA, B(a)P, 2-NF, NaNo2) controls run to validate method. All assays run in triplicate. Bartletts' test for homogeneity of variance and group-wise comparisons made within levels of pooled variance, 1-sided t-test applied, $p<0.05$. For positives, Grubb's test run to determine outliers and regression analysis and t-test of transformed data to determine dose response.
Result : Negative in all 4 test strains, with and without activation, up to max. conc. of 25 mg/spot in Spot test.
Positive finding only with TA98 (statistically elevated without activation and elevated, but not statistically with activation) in plate incorporation assay; all other strains were negative with and without activation
Test substance : Technical grade PNA with purity of > 99%.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
28.08.2002 (13)

Type : Cytogenetic assay
System of testing : Chinese Hamster Ovary cell culture
Concentration : 50 to 5000 ug/mL
Cycotoxic conc. : Laboratory 1 - 1600 ug/ml and higher; laboratory 2- none up to 5000 ug/ml
Metabolic activation : with and without
Result : ambiguous
Method : other
Year : 1986
GLP : no data
Test substance : other TS
Method : NTP study design, exposing cells for 8 -12 hr nomally and for 2hr in presence of S9; 100 cells per dose group were scored, all types of aberrations were recorded; Dunnett's adjusted P value ($p<0.05$) was used for statistical assessment.

Result	:	Two separate testing labs used, each giving nonconfirmatory results. Positive results reported with S9 in studies at laboratory 1, and weak positive without S9 at Lab 2, Effects only seen at very highest test levels, with no evaluation of influence of pH or osmolarity. Cytotoxicity observed at Lab 1 but not reported at lab 2.
Test substance	:	Reportedly commercially available; i.e. technical grade of > 99%
Reliability	:	(3) invalid Results considered ambiguous. Inconsistency of positive findings renders results i nconclusive; additional concerns regarding inconsistency in cytotoxicity seen within lab trials and between labs. No effort made to determine affect, if any, of pH or osmolarity changes on study outcome. Supplemental HPV study since a fully acceptable in vivo micronucleus test fulfills this HPV Endpoint.

07.11.2002 (5)

Type	:	Cytogenetic assay
System of testing	:	CHO-K1 (Chinese Hamster Ovary) cells
Concentration	:	173, 345, 690, and 1035 ug/ml
Cycotoxic conc.	:	none observed
Metabolic activation	:	without
Result	:	ambiguous
Method	:	other
Year	:	1996
GLP	:	no data
Test substance	:	other TS
Method	:	Unique, research methodology performed. Used established cell line without incorporation of S9 fraction as data included in this paper considered PNA as a weak, direct acting mutagen in an Ames/Salmonella test. After incubation for 2 hrs with test compound dissolved in DMSO, cells were washed twice with PBS and incubated for another 20 hr in fresh medium. After colchicine addition, and three further hrs of incubation, metaphase cells were harvested by mitotic shake-off and resuspended. Cells were fixed, stained and selected for analysis. At least 100 metaphases per flask were scored for each dose for individual types of aberrations, including breaks, deletions, exchanges and dicentrics. Both the percentage of aberrant cells and the frequency of aberrations were calculated. The tests were repeated three times in total such that at least 300 metaphases were scored for each dose. A positive response was determined based on the percentage of cells with aberrations showing a dose-response trend and at least a four-fold increase over that of the negative controls at one or more doage levels. Both Eagles' basal medium and DMSO were tested as negative controls. TEM served as a positive control.
Result	:	The results obtained are considered ambiguous since specified criterion for determination of a positive response (4X % aberrant cells over negative control-in this case DMSO) were not met. Neither the positive control (0.25 ug/ml TEM) nor any of the PNA dose levels exhibited a 4X increase from the negative DMSO control; the positive control and all PNA dose levels did exhibit a 4X increase in aberrant cells over the Eagle's medium negative control. The % aberrant cells reported were: Eagle's medium (3), DMSO (6), TEM (22), 173 ug/ml PNA (13), 345ug/ml PNA (19), 690 ug/ml PNA (20), and 1035 ug/ml PNA (20).
Test substance	:	Obtained commercially (Sigma Chem.), and thus technical grade of > 99%.
Reliability	:	(3) invalid Supplemental HPV study since a fully acceptable in vivo micronucleus test is available to fullfill this endpoint; also ambiguous outcome of this study renders it unuseable.

07.11.2002 (2)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Micronucleus assay
Species	:	mouse
Sex	:	male/female
Strain	:	CD-1
Route of admin.	:	i.p.
Exposure period	:	two doses, 24-hours apart
Doses	:	80, 400 and 800 mg/kg
Result	:	negative
Method	:	OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year	:	1987
GLP	:	yes
Test substance	:	other TS
Method	:	High dose considered to be 80% of IP LD50, as determined by preliminary study using probit method; corn oil used as vehicle (10 ml/kg); 12 mice/sex were used for the 800 mg/kg test group, 5/sex at 400 and 80 mg/kg and 10/sex for the untreated control group; Doses were administered by IP twice with 24 hr separating each dose. Bone marrow was taken after 24 and 48 hr following last treatment from HD and C mice and after 24 h from mid and low dose animals; all mice were observed daily for clinical signs. Micronuclei recorded after assessment of 1000 PCEs/mouse at all test levels; cyclophosphamide (40 mg/kg, twice) used as positive control. Statistical significance was determined by Student's t-test (1-sided), $p<0.05$.
Result	:	No increases were seen in micronucleated PCE frequency in any PNA test group; toxicity to the cell population observed at 800 mg/kg @ 48h interval; elevated incidence of micronuclei with the positive control confirmed validity of method. One death and clear signs (unresponsiveness and tremors up to 4 hr after dosing) of toxicity were noted at 800 mg/kg; at 400 mg/kg - listlessness and some tremors seen occasionally after dosing; 80 mg/kg - listlessness immediately after dosing; No effects on body weight were observed at any test level.
Test substance	:	Technical grade PNA with purity > 99%.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

16.10.2002 (15)

04.04.2002

5.7 CARCINOGENITY

5.8 TOXICITY TO REP RODUCTION

Type	:	Two generation study
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	F0 & F1 Adults-premating through litter weaning(F0) and postweaning (F1)
Frequency of treatment	:	daily (7d/wk) gavage
Premating exposure period		
Male	:	F0- 14 weeks; F1 - 18 weeks
Female	:	F0- 14 weeks; F1 - 18 weeks

Duration of test	:	F0 M/F -167d; F1 M/F - 216d
Doses	:	0, 0.25, 1.5 and 9 mg/kg/d
Control group	:	yes, concurrent vehicle
NOAEL Parental	:	>= 9 mg/kg bw
NOAEL F1 Offspr.	:	>= 9 mg/kg bw
Method	:	OECD Guide-line 416 "Two-generation Reproduction Toxicity Study"
Year	:	1983
GLP	:	yes
Test substance	:	other TS
Method	:	Test material was given to groups of 15M and 30F rats (vehicle control group also included) to F0 and F1 generations during a premating (14 wks for F0 and 18 wks for F1) growth period, and through the ensuing mating, gestation and lactation intervals (1 litter/generation). F1 rats continued on treatment during a post-weaning period of 30d. Dosing concentrations confirmed for accuracy Body weights were recorded weekly for F0 and F1M. For F0 and F1 F wts were recorded weekly through the growth period and up to mating, then resumed after mating until sacrifice. Food consumption was recorded weekly for F0 and F1 M from study start up to mating, then resumed after mating through study term. Food consumption for adult females F0 and F1 was recorded weekly through the growth period and again after weaning of litters. Cageside observations were made weekly, as well as daily observations of clinical signs. Temperature, humidity and light-dark cycles were controlled. F0 adults were sacrificed following weaning of the F1 litters and given a gross postmortem examination; reproductive tissues (testes, epididymides, seminal vesicles) were evaluated histopathologically for all control and high dose males. Adult M and F rats were sacrificed following completion of a post-weaning treatment interval, given a gross necropsy, and full histopathological examination of over 40 tissues and organs (including gonads) performed on 10 randomly selected animals/sex/group. Pups delivered to F0 and F1 females were evaluated for growth, survival and external irregularities during lactation days 0, 4, 14 and 21. F1 pups not selected for the adult generation were sacrificed and given a gross postmortem exam. Tissues were evaluated histopathologically (~40 tissues/organs) from 5/sex/group of F1 pups.
Result	:	No adverse effects observed in either F0 or F1 adults in mortality, body weights or food consumption or physical in-life evaluations. Mating indices were comparable to controls for both F0 and F1. A statistically significant reduction in pregnancy rate was observed in the 9 mg/kg F0 group vs concurrent control value, and just outside of laboratory historical control range. The male fertility index was slightly, but not statistically, lower at 9 mg/kg dose in F0. Both male and fe male fertility indices in F1 generation were comparable to control group at all test levels. No adverse effects were observed in mean length of gestation, no. live and dead pups at monitored time points, pup weights during lactation, pup and litter surviva l. No compound-related gross postmortem changes were observed during examination of any F0 or F1 adults or offspring. No microcopic changes were noted with respect to gonads evaluated on F0 adults or F1 offspring.
Test substance	:	Technical grade PNA with purity > 99%.
Conclusion	:	The reduction in female fertility index seen in F0 adults is considered unrelated to treatment for the following reasons: No similar findings occurred in F1 Females, even though they were exposed for a substantially longer period (both in utero and during premating phase) than their F0 counterparts and there was no evidence of histological changes in gonads which could account for this finding; Similarly, no treatment-related effects were observed on the gonads of rats exposed for up to 2 years by the same dosage (9 mg/kg/d) by the same exposure route (gavage) (Nair et al FAAT 15:607-621)
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

16.10.2002 (11)

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	gestation days 6 through 19
Frequency of treatment	:	once per day, gestation days 6-19
Duration of test	:	dosing during gestation days 6-19, sacrificed on day 20
Doses	:	0, 25, 85, 250 mg/kg
Control group	:	yes, concurrent vehicle
NOAEL Maternalt.	:	= 25 mg/kg bw
NOAEL Teratogen	:	= 85 mg/kg bw
NOAEL Embryotoxicity	:	= 85 mg/kg bw
NOAEL Fetotoxicity	:	= 25 mg/kg bw
Method	:	OECD Guide-line 414 "Teratogenicity"
Year	:	1980
GLP	:	yes
Test substance	:	other TS
Method	:	24 pregnant female rats per group; dosing occurred during days 6-19; vehicle used was corn oil (10 ml/kg constant volume), Corn oil vehicle control also included. Nidation data collected at sacarifice; live fetuses examined externally and by Wilson sections and skeletal exam techniques used to detect any variations or abnormalities. Body weights collected on gestation days 3, 6, 8, 13, 15, 17 and 20. Statistical methods used: body wts analyzed using Dunnett's test, Counted data (corpora lutea, implants, resorptions, live/dead pups) were analyzed using Mann-whitney U test; Response data (eg. pregnancy rates, litters with postimplantation loss, etc.) assessed with Fischer's exact test and Chi square test. ($p<0.05$ and $p<0.01$),
Remark	:	Supplemental information for HPV program as an adequate 2-generation study is available on PNA to fulfill the Reproductive Toxicity Endpoint.
Result	:	250 mg/kg: Reduced maternal wt gain between d6-d20, observations - pale eye coloration and occasional convulsions after dosing, significant increase in mean no. resoprtions and % resorptions, significant increase in maternal mean spleen wts (abs. and rel), significantly lower mean fetal wts (both sexes), significant increase in no. fetuses with ossif. variations and fetuses with external, soft tissue or skeletal malformations (predominantly kinked or shortened tail, absence of kidneys or ureter and fused ribs); 85 mg/kg - Significant increase in mean maternal spleen wts, significantly lower mean fetal wts (both sexes); no increases in variations or malformations; 25 mg/kg - no effects on maternal, embryo- or fetotoxicity and no increase in malformations; 25 mg/kg - no treatment-related effects on maternal, embryotoxicity, fetotoxicity or terata.
Test substance	:	Technical grade PNA with purity > 99%.
Reliability	:	(1) valid without restriction

28.08.2002 (18)

Species	:	rabbit
Sex	:	female
Strain	:	New Zealand white
Route of admin.	:	gavage
Exposure period	:	gestation days 7 through 19
Frequency of treatment	:	daily
Duration of test	:	dosed from gestation day 7 through 19, sacrificed on g. day 30
Doses	:	0, 15, 75, 125 mg/kg
Control group	:	yes, concurrent vehicle
NOAEL Maternalt.	:	= 75 mg/kg bw
NOAEL Teratogen	:	= 125 mg/kg bw

NOAEL Embryotoxicity	:	= 125 mg/kg bw
NOAEL Fetotoxicity	:	= 125 - mg/kg bw
Method	:	OECD Guide-line 414 "Teratogenicity"
Year	:	1981
GLP	:	yes
Test substance	:	other TS
Method	:	18 mated females used per dose group; vehicle used was corn oil. Treated and control groups (corn oil) were dosed at constant volume of 2 ml/kg; Observations made for signs of toxicity on gestation days 0, 7, 10, 15, 19, 25 and 30; Body weights recorded on gestation days 0, 7, 19 and 30. Nidation data collected at sacrifice (gestation day 30). live fetuses examined externally and by Wilson sections and skeletal exam techniques to detect any variations or abnormalities. Statistical methods used: Bartlett's and ANOVA, Dunnett's test , Mann-whitney U test, Dunn's Rank Sum, Fischer's exact test and Jonckheere's test; $p<0.05$ and $p<0.01$.
Remark	:	Supplemental information for HPV program as an adequate 2-generation study is available on PNA to fulfill the Reproductive Toxicity Endpoint.
Result	:	125 mg/kg - 7/18 deaths between gestation days 14 and 20, observations - grayish appearing eyes; overall body wt gain similar to controls but higher no. of animals which lost wt during dosing observed at this test level; no increase in absol or rel spleen wt; incidence of spontaneous abortions was 4 (vs 2 for controls), however, this incidence level was frequently seen with rabbits at the test facility and thus could not be attributed to test article; no significant differences observed in mean no. implantations, resorptions or viable fetues or mean fetal wts between treated and control group; incidence and types of ossification variations in fetuses , soft tissue anomalies and external malformations were similar between treated and control groups; a slightly higher (not statistically significant) incidence in skeletal malformations was observed in treated groups vs. controls but was not considered treatment related as there was no dose response relationship for individual malformations identified in this study and they have been observed as spontaneous lesions in this rabbit strain; 75 mg/kg: observations - grayish eyes, otherwise no effects on other measured maternal, embryo, or fetal parameters. No evidence of treatment-related effect on variations or malformations; 15 mg/kg - no treatment related study findings
Test substance	:	Technical grade PNA with purity of > 99%.
Reliability	:	(1) valid without restriction

07.11.2002 (12)

05.04.2002

05.04.2002

5.10 OTHER RELEVANT INFORMATION

5.11 EXPERIENCE WITH HUMAN EXPOSURE

(1) Budavari, S. (ed.) 1989. The Merck Index. - an encyclopedia of chemicals, drugs and biologicals, Whitehouse, NY. p.1042.

(2) Chung, K-T, Murdock, CA, Yanggui, Z, Stevens, Jr, SE, Li, Y-S, Wei, C-I, Fernando, SY and Chou, M-W. 1996. Effects of the nitro-group on the mutagenicity and toxicity of some benzamines. Environ Molec. Mutagen. 27:67-74.

(3) Dixon and Rissmann. 1985.

(4) EPIWIN, version 3.10. 2002. Syracuse Research Corp., Syracuse, NY.

(5) Galloway, SM, Armstrong, MJ, Reuben, C, Colman, S, Brown, B, Cannon,C, Bloom, AD, Nakamura, F, Ahmed, M, Duk, S, Rimpo, J, Margolin, BH, Resnick, MA, Anderson, B, and Zeiger, E. 1987. Environ Molec Mutagenesis 10:1-175..

(6) Hansch and Leo, 1987. The Log P Database. Claremont, Ca: Pomona College.

(7) Lu, G.-H, Yuan, X, and Zhao, Y-H. 2001. Chemosphere 44:437-440.

(8) Solutia study BD-80-508. A four-week inhalation toxicity study of para-Nitroanaline in the rat; also published as Nair et al. (1986) Fundamen Appl Toxicol 6:618

(9) Solutia study no. AB-80-318. Acute toxicity of para-Nitroaniline to Rainbow Trout.

(10) Solutia study no. AB-80-320. Acute toxicity of p-Nitroaniline to Daphnia magna.

(11) Solutia study no. BD-80-471. A 2-generation reproduction study of p-Nitroaniline in rats; also published as Nair, RS et al. 1990. FAAT 6:607-621.

(12) Solutia study no. BD-80-529; also published as Nair, RS et al 1985 in Toxicology of Nitroaromatic Compounds. Hemisphere Publishing, NY.

(13) Solutia study no. DA-79-257. Salmonella mutagenicity assay of CP 26926 (p-Nitroaniline). [EPA Documentation No. 878211039; Fiche No. OTS0206222].

(14) Solutia Study no. ML-79-11. Ninety-day study of p-Nitroaniline administered to male and female Sprague-Dawley rats via gavage; also Houser, TAP 3:128

(15) Solutia study no. ML-87-8. Mouse micronucleus assay with p-Nitroaniline.

(16) Solutia study no. MO20020140. Biodegradation testing of o-Nitroaniline and p-Nitroaniline.

(17) Solutia study no. Y-76-35. Toxicological Investigaion: P-Nitroaniline.

(18) Study no. BD-79-326; also published as Nair, RS et al 1985 in Toxicology of Nitroaromatic Compounds. Hemisphere Publishing, NY.

(19) Suzuki. J. 1991. J. Computer-Aided Molecular Design 5: 149-166.

7.1 END POINT SUMMARY

7.2 HAZARD SUMMARY

7.3 RISK ASSESSMENT